Biology Library
Bio.

December 1960 · VOL. 19 · No. 4 · PUBLISHED IN THREE PARTS

PART II
Supplement no. 5

Federation Proceedings

Proceedings of a Symposium held in
BUENOS AIRES
AUGUST 5–7, 1959

Biology Library

COLD ACCLIMATION

Published quarterly by the
FEDERATION *of* AMERICAN SOCIETIES
for EXPERIMENTAL BIOLOGY

XUM

FEDERATION PROCEEDINGS DECEMBER 1960

Supplement no. 5

PROCEEDINGS OF THE

INTERNATIONAL SYMPOSIUM ON COLD ACCLIMATION

Instituto Antártico Argentino

Buenos Aires, August 5–7, 1959

ROBERT E. SMITH *Editor-in-Chief*
DOROTHY J. HOIJER *Executive Editor*

Associate Editors

RALPH BRAUER OLIVIER HEROUX
LAURENCE IRVING KARL M. KNIGGE

Published by the

FEDERATION of AMERICAN SOCIETIES for EXPERIMENTAL BIOLOGY

XUM

© *Copyright 1960 by*

FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY

PRINTED IN THE UNITED STATES OF AMERICA
BY WAVERLY PRESS, INC., BALTIMORE, MARYLAND

Preface

THE current Supplement to the *Federation Proceedings* presents the Proceedings of the International Symposium on Cold Acclimation, organized under the joint sponsorship of the Instituto Antártico Argentino and the Federation of American Societies for Experimental Biology, and held August 5–7, 1959, in Buenos Aires, Argentina.

This undertaking and the current publication were made possible only through the active cooperation of the participants and the generous support of their own institutions and by the United States Air Force Office of Scientific Research, the United States Army Quartermaster Research and Engineering Command, the United States Department of the Navy Office of Naval Research, the National Science Foundation, and Burroughs Wellcome and Company (USA), Inc. These are in addition to essential services provided by the Instituto Antártico Argentino, including bilingual printed programs, tape recordings and transcriptions of the discussions and a most impressive banquet held in honor of the participants. To the good offices of these agencies and the faith of their representatives must go the gratitude not only of the participants, but of the many who, it is believed, will share through the present publication some measure of the scientific results of this effort.

To the late Professor Eduardo Braun-Menéndez must go the major credit for implementing this Symposium by engaging at the outset the active interest and effective support of Rear Admiral Rodolfo N. M. Panzarini, Director del Instituto Antártico Argentino in Buenos Aires. The Symposium thus acquired the mutual support of both the Instituto Antártico Argentino and the Executive Committee of the XXI International Congress of Physiological Sciences, and to all parties thereof it remains greatly indebted for the success of the venture. Specific acknowledgment is due to the Congress President, Professor Dr. Houssay, to Professor Dr. Stoppani, and especially to the Congress Treasurer, Professor Dr. Enrique Strajman, who somehow managed to find time to discharge the further duties of Organizing Cochairman for the Cold Symposium. From these men, and from Admiral Panzarini, our thoughtful host, the participants were to carry back to their far-flung homelands some important lessons in the quality and meaning of the words "men of good will."

As in all joint efforts of this nature, there will always be the silent soldiers who secure the passage. High among these in our support stood the Organizing Committee, including Doctors Loren D. Carlson in Seattle, O. G. Edholm in London, J. Sanford Hart in Ottawa and E. A. Sellers in Toronto. Grateful acknowledgments go as well to Dr. Milton O. Lee, Administrative Assistant Ann Nixon and Business Manager Robert H. Harvey of the Federation Office, and to Doctors Orr E. Reynolds, Paul Siple, John Talbott and Frank Fremont-Smith, all of whom have guided our destinies through crucial phases of this endeavor. In the office of the Symposium editors Mrs. Barbara Jacobsen has rendered invaluable service.

ROBERT E. SMITH
Editor-in-Chief

XUM

THIS SYMPOSIUM was sponsored by the Federation of American Societies for Experimental Biology and the Instituto Antártico Argentino and was supported by funds from the United States Air Force Office of Scientific Research, the United States Army Quartermaster Research and Engineering Command, the United States Department of the Navy Office of Naval Research, the National Science Foundation, and Burroughs Wellcome and Company (USA), Inc.

A Spanish-language edition of the *Proceedings of the International Symposium on Cold Acclimation* is being prepared for publication in the near future under the auspices of the Instituto Antártico Argentino.

Contents

Preface iii
Participants vii
Welcoming address — Rear Admiral Rodolfo N. M. Panzarini 1
Introductory statement; outline of objectives — Robert E. Smith 2

I

Man in a Cold Environment

Chairman: E. F. Adolph

Polar physiology — O. G. Edholm 3
DISCUSSION — P. F. Scholander 8
Commentary on antarctic operations — Paul Siple 10
DISCUSSION 11
Summary — Laurence Irving 12

II

Thermogenesis in the Acclimated Animal

Chairman: Laurence Irving

Energy metabolism during exposure to cold — J. S. Hart 15
Calorigenesis from various organ systems in the whole animal — Florent Depocas 19
DISCUSSION 25
Nonshivering thermogenesis and its endocrine control — L. D. Carlson 25
Peripheral and central control of cold-stimulated thermogenesis — Allen D. Keller 30
The sensory receptor organ and quantitative mechanism of human temperature control in warm environment — T. H. Benzinger 32
DISCUSSION 41
Summary — O. Heroux 43

III

Neurohumoral Response Patterns and Endocrine Functions

Chairmen: Allen D. Keller, E. D. P. De Robertis and L. P. Dugal

Neuroendocrine mechanisms influencing ACTH and TSH secretion and their role in cold acclimation — Karl M. Knigge 45
Adenohypophysial function in the guinea pig at low environmental temperature — S. A. D'Angelo 51
DISCUSSION 56
Role of thyroid secretion in cold acclimation — Walter H. Cottle 59

XUM

Comparative effects of thyroxin *in vivo* and cold acclimation on metabolic activity of cell fractions from rat liver — Robert E. Smith 64
Submicroscopic analysis of the secretory process in the adrenal medulla — E. D. P. De Robertis and D. D. Sabatini 70
Exposure to cold and catecholamines — U. S. von Euler 79
Adjustments of the adrenal cortex and thyroid during cold acclimation — O. Heroux 82
Adrenocortical function in rats exposed to low environmental temperatures — E. Schönbaum 85
Ascorbic acid in cold acclimation — André DesMarais 88
Metabolic function of ascorbic acid in acclimation to cold — Dorothy Jared Hoijer 90
Relation of ascorbic acid to adrenocortical function during cold stress — W. M. Booker 94
DISCUSSION 96

IV

Intermediary Metabolism

Chairman: A. O. M. Stoppani

Intermediary glucose metabolism in the cold-acclimatized rat — John P. Hannon 100
Glucose metabolism in warm- and cold-acclimated rats — Florent Depocas 106
Cold exposure and the immune response — Ignatius L. Trapani 109
Alterations in hepatic lipid metabolism induced by acclimation to low environmental temperatures — E. J. Masoro 115
Metabolism of serum-free fatty acids — R. S. Gordon, Jr. 120
Comments on intermediary metabolism in relation to cold — R. B. Mefferd, Jr. 121
Effects of exposure to cold on coenzyme *A* levels in liver tissue — J. Campbell, G. R. Green, E. Schönbaum and H. Socol 124
Influence of cold exposure on electrolyte metabolism — D. G. Baker 125
Electrolytes in acclimation to cold — W. S. Platner 130
DISCUSSION 131
Editor's summary — R. W. Brauer 135

V

Cellular and Subcellular Energetics

Chairman: L. F. Leloir

Factors which affect cold acclimatization — A. K. Weiss 137
Tissue energy metabolism in the cold-acclimatized rat — John P. Hannon 139
Comments on oxidative phosphorylation in relation to cold acclimation — Robert E. Beyer 145
Mitochondrial control of oxidative phosphorylation in cold-acclimated rats — Robert E. Smith 146
Summary — Robert E. Smith 152

VI

General Discussion and Summary of the Symposium

Chairman: Frank Fremont-Smith

General discussion 155
Summary of the Symposium — Dorothy Jared Hoijer and Robert E. Smith 162
Concluding address — Rear Admiral Rodolfo N. M. Panzarini 165

Participants

E. F. Adolph	Department of Physiology, University of Rochester, Rochester, New York
D. G. Baker	C. H. Best Institute, Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada
T. H. Benzinger	Naval Medical Research Institute, National Naval Medical Center, Bethesda, Maryland
Robert E. Beyer	Department of Physiology, Tufts University School of Medicine, Boston, Massachusetts
W. M. Booker	Department of Pharmacology, Howard University Medical School, Washington, D. C.
R. W. Brauer	Naval Radiological Defense Laboratory, San Francisco, California
L. D. Carlson	Department of Physiology and Biophysics, University of Washington School of Medicine, Seattle, Washington
Merva Cottle	Department of Physiology and Pharmacology, University of Alberta, Edmonton, Canada
Walter H. Cottle	Department of Physiology and Pharmacology, University of Alberta, Edmonton, Canada
S. A. D'Angelo	Daniel Baugh Institute of Anatomy, Jefferson Medical College, Philadelphia, Pennsylvania
Florent Depocas	Division of Applied Biology, National Research Council, Ottawa, Canada
E. D. P. De Robertis	Instituto de Anatomía General y Embriología, Facultad de Ciencias Médicas, Buenos Aires, Argentina
André DesMarais	Department of Biology, University of Ottawa, Ottawa, Canada
L. P. Dugal	Department of Biology, University of Ottawa, Ottawa, Canada
O. G. Edholm	Division of Human Physiology, Medical Research Council, London, England
I. G. Fletcher	Department of National Defense, Toronto, Canada
Frank Fremont-Smith	Josiah Macy, Jr. Foundation, New York City
E. M. Gal	Department of Pharmacology, University of California Medical School, Los Angeles, California
R. S. Gordon, Jr.	Laboratory of Cellular Physiology and Metabolism, National Heart Institute, Bethesda, Maryland
H. T. Hammel	Department of Physiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania
John P. Hannon	Physiology Department, Arctic Aeromedical Laboratory, APO 731, Seattle, Washington
J. S. Hart	Division of Applied Biology, National Research Council, Ottawa, Canada

XUM

O. Heroux	Division of Applied Biology, National Research Council, Ottawa, Canada
Dorothy Jared Hoijer	Department of Physiology, University of California School of Medicine, Los Angeles, California
Bernardo Houssay	Facultad de Ciencias Médicas, Universidad de Buenos Aires, Buenos Aires, Argentina
Laurence Irving	Arctic Health Research Center, Department of Health, Education and Welfare, Anchorage, Alaska
Charles Kayser	Institut de Physiologie, Faculté de Médecine, Strasbourg, France
Allen D. Keller	Physiology Division, U. S. Army Medical Research Laboratory, Fort Knox, Kentucky
Karl M. Knigge	Department of Anatomy, University of Cincinnati College of Medicine, Cincinnati, Ohio
L. F. Leloir	Instituto de Investigaciones Bioquímicas, Buenos Aires, Argentina
E. J. Masoro	Department of Physiology, Tufts University School of Medicine, Boston, Massachusetts
R. B. Mefferd, Jr.	Psychiatric and Psychosomatic Research Laboratory, Houston Veterans Administration Hospital, Houston, Texas
Lj. Mikailovic	Institute of Pathology, Belgrade University Medical School, Belgrade, Yugoslavia
M. F. Morales	Department of Biochemistry, Dartmouth Medical School, Hanover, New Hampshire
Nello Pace	Department of Physiology, University of California, Berkeley, California
W. S. Platner	Department of Physiology, University of Missouri School of Medicine, Columbia, Missouri
D. D. Sabatini	Instituto de Anatomía General y Embriología, Facultad de Ciencias Médicas, Buenos Aires, Argentina
P. F. Scholander	Scripps Institution of Oceanography, La Jolla, California
E. Schönbaum	Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada
E. A. Sellers	Department of Pharmacology, University of Toronto, Toronto, Canada
Paul Siple	Office of Chief of Research and Development, Army Research Office, Washington, D. C.
Robert E. Smith	Department of Physiology, University of California School of Medicine, Los Angeles, California
A. O. M. Stoppani	Facultad de Ciencias Médicas, Universidad de Buenos Aires, Buenos Aires, Argentina
E. Strajman	Facultad de Ciencias Médicas, Universidad de Buenos Aires, Buenos Aires, Argentina
Ignatius L. Trapani	Department of Experimental Immunology, Research Institute, National Jewish Hospital, Denver, Colorado
U. S. von Euler	Fysiologiska Institutionen, Karolinska Institutet, Stockholm, Sweden
A. Kurt Weiss	Department of Physiology, University of Miami School of Medicine, Coral Gables, Florida

Welcoming address

REAR ADMIRAL RODOLFO N. M. PANZARINI
Instituto Antártico Argentino, Buenos Aires, Argentina

IT IS VERY PLEASANT for me to extend a welcome greeting to the distinguished investigators in the field of physiology who, coming from different countries, meet here for the International Symposium on Cold Acclimation.

The selection of the premises of the Argentine Antarctic Institute for the purpose of conducting this Symposium is in agreement with its character as a scientific and technical organization having the object of studying the nature of the Antarctic. It is thus directly interested in the investigation of human reactions in climates of low temperature as one of the many topics regarding the processes that manifest themselves as belonging to the polar environment with which it is concerned.

This Institute is therefore intended to carry out Antarctic research in all the natural sciences within the frame of pure science; to develop and use in what is related to polar technique, the principles, rules, material means and forms to be employed to arrive at, remain and travel in a polar region; and to transmit to specialists and the general public knowledge of the nature of the Antarctic and the essence of its problems.

To fulfill these purposes, the Ellsworth Scientific Station, located on the Filchner ice shelf in the Weddell Sea, is administered and operated; specialized personnel are sent to different permanent antarctic bases on board the ships of the expedition that is annually organized by the Argentine Navy. Several groups of scientists go every summer to the Antarctic for field work; laboratories and scientific equipment are available in this building for the analysis of the data collected, and agreements with other scientific organizations are made to carry out joint research projects. The results accomplished are regularly published and a varied cultural activity is carried on.

As it is only three years since this organization was started, having to do everything necessary in this inadequate building, its staff of 14 scientists and 21 technicians having been formed only two and one half years ago, the specific research work of the Institute is just beginning. During this period of organization and installation of the required equipment some work has, however, already been done; 5 books and 24 papers have been published, and as many are at present in the press or in preparation.

I wish to thank the Federation of American Societies for Experimental Biology for having bestowed upon the Argentine Antarctic Institute the honor of selecting it as the place where this Symposium is to be held, and I also wish to thank the participants for their contribution to its successful materialization.

XUM

Introductory statement

Outline of objectives of the Symposium

ROBERT E. SMITH
Department of Physiology, University of California Medical School, Los Angeles, California

THE PRESENT International Symposium on Cold Acclimation convening here in Buenos Aires represents an heuristic culmination of much that has gone before it. Many of the participants here on this occasion have contributed in diverse ways to the history and creation of earlier convocations of this sort. Notable among these has been the recently concluded 6-year series of Conferences on Cold Injury under the sponsorship of the Josiah Macy, Jr. Foundation and the skilled guidance of Dr. Frank Fremont-Smith. These have added much not only to the definition of the problems in the area of cold injury, but as well to the development of basic thinking on the questions of acclimatization of man and animals to cold environments. An expression of this need has emerged at several of the past International Physiological Congresses and given rise to informal gatherings of varying size and ranges of interests. More recently, Dr. Loren Carlson arranged a short symposium at Philadelphia in April 1958, which brought new data and concepts to bear on the problems of organ and cell thermogenesis (*Fed. Proc.* 17: 1044, 1958). In this he employed the principle which has been followed here as well, namely that of bringing in some contributors representative of allied disciplines in order to provide the basis for new points of approach.

The Agenda of the Symposium will center around the basic response patterns of man and animals to continued exposure to low environmental temperatures. A serious attempt will be made to achieve a systematic coverage of adaptive behavior (particularly heat production) of the intact organism in terms of the known regulatory mechanisms operating variously in organ systems at cell and subcellular levels. The stimulus-response pattern to chronic exposure to cold will be examined in respect to its components of mediation by the central nervous system through somatic, autonomic and neurohumoral outflows. Primary and secondary responses at organ and tissue levels will be related wherever possible to target effects of these regulatory modalities on cell and subcellular behavior. The latter must in turn be associated with quantitative and qualitative alterations in substrate utilization and preferred metabolic pathways within the cells. Since the most challenging hiatus currently lies in just this area, there is a genuine need for the integration of these biochemical interactions with the corresponding physiological response patterns.

In view of our limits of knowledge and the enormous complexity of these interactions, this integration presents a formidable and extensive task; the more so because of the diverse specialisms which must be embraced and amalgamated in the process.

Whence it is a primary objective of the present Symposium to convene a representative group of qualified specialists and to facilitate thereby the definition of their common problems in mutually acceptable terms.

I

Man in a Cold Environment

Chairman: E. F. ADOLPH

Polar physiology

O. G. EDHOLM
Division of Human Physiology, National Institute for Medical Research, Medical Research Council, London, England

ACCLIMATIZATION OF MAN TO COLD has been studied in climatic chambers and in the field. In order to evaluate the results obtained so far it is necessary to define the conditions in which experiments can be made. The results of observations on man in cold chambers have been equivocal, with the important exception of the demonstration by Mackworth (1) of the phenomenon of local acclimatization of the hands. However, subjects can only be kept for a limited time in a cold room, and it is quite possible that physiological adaptation to cold may not develop for many weeks or months.

Field work can involve the study of people permanently inhabiting cold places, such as the Eskimo or the Lapp or other more primitive people, who live in conditions of moderate cold with little or no clothing, such as the Australian aborigine or the Bushman of the Kalahari. In recent years Scholander and his colleagues (2) have studied the Lapp and the Australian aborigine, Wyndham and Morrison (3) have observed the Bushman, and there have been extensive studies on the Eskimo.

Another group can be studied in the field: men going from temperate countries on expeditions to polar regions. Work in the Medical Research Council, Division of Human Physiology, London, has been concentrated on this aspect (4). It began in 1952, when it proved possible to persuade the British North Greenland Expedition to include a physiologist as well as a medical officer, and to recognize physiology as a proper subject to study on a polar expedition. Dr. H. E. Lewis was appointed and with Dr. J. P. Masterton, the medical officer, formed a joint medical and physiological team. Amongst the subjects they studied were the sledging rations, and on the return of the expedition to London in 1954, Lewis and Masterton devised a new sledging ration which the Falkland Islands Dependencies Survey (F.I.D.S.) decided to try.

This was the beginning of a close association between the F.I.D.S. and the Division of Human Physiology. Three or four medical officers are appointed each year to serve for 1–2 years at a base on Graham Land or one of the associated islands. A number of these medical officers have had preliminary training in simple physiological techniques before going south and have obtained valuable data (fig. 1).

The 1st-year party of the Trans-Antarctic Expedition left England in the autumn of 1955, with Dr. Rainer Goldsmith as medical officer and physiologist. These men spent a year in Antarctica at Shackleton (fig. 1) in very severe conditions owing to various mishaps, but Goldsmith was able to make regular observations. At the end of 1956, the main party left England with Dr. Alan Rogers, Lecturer in Physiology at Bristol University, acting as medical officer.

In 1955, also, the Royal Society base, in connection with the International Geophysical Year, was set up at Halley Bay. This base has now been taken over by the Falkland Islands Dependencies Survey, and observations have been continued by the medical officers stationed there.

In general, the observations have followed the same lines as those of Lewis and Masterton (5), who *inter alia* measured basal metabolic rate, food intake and energy expenditure, fat absorption, body weights, skin-fold thickness and sleep rhythms. In addition, clothing records have been kept at a number of bases, and recently Adam and Pugh, from this Laboratory, have made measurements of energy expenditure and skin temperature at Scott Base (fig. 1).

In Greenland, the basal metabolic rate was measured at regular intervals, approximately once a month on some 20 men for a year, and on some for 2 years. There were considerable fluctuations amongst the subjects, but there was no significant rise associated with the winter;

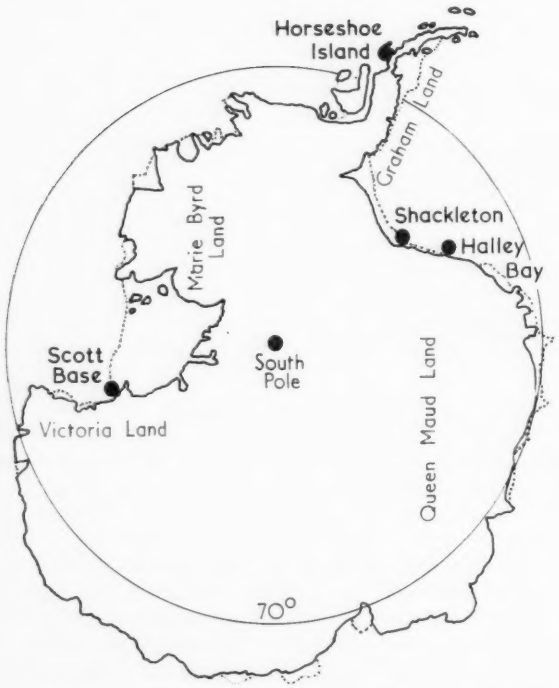


FIG. 1. Map of the Antarctic Continent giving the location of bases at which physiological observations have been made.

both the intersubject and intrasubject variation were much larger than any effect which might be attributed to season. When this study was being prepared for publication, it was found that no comparable study of the variation in the basal metabolic rate with time appears to have been made in temperate countries, or indeed in any country. This is one of the reasons that has led us to believe that the study of young men living in isolation at high latitudes may not necessarily teach us much about the effects of cold but does provide remarkable opportunities for studying fundamental human biology. Not only is there a captive group of subjects, but also a captive physiologist.

To return to the basal metabolic rate, whatever else might have been demonstrated, it seemed pretty clear that there was no increase in basal metabolic rate due to the cold environment. Dr. Ove Wilson, of the Norwegian-Swedish-British Expedition to Mandheim, has obtained similar results (6).

Body weight and skin-fold thickness were also regularly measured in Greenland. It was thought that a possible mechanism of acclimatization might be demonstrated by an increase in the thickness of the subcutaneous fat, with an increased body insulation. The results did indeed show a seasonal change, with some increase in the winter and a decrease in the summer; although these changes were not large they were significant. Again it has proved difficult to find comparable records over periods of a year or more, in regions other than polar. But the records of body weights of recruits to the British Army who are admitted at intervals of 2 weeks throughout the year have been examined by Rosenbaum (7) and no evidence of any seasonal trend was found.

In all the records from the Antarctic examined so far, a seasonal change in body weight and skin-fold thickness has been observed. There is one exception, the members of the 1st year of the Trans-Antarctic Expedition. In this year conditions were exceptionally severe, as there was a shortage of fuel, and food had to be rationed; in addition, the men had to work hard throughout the winter (8). Weight was lost during the winter and recovered during the 'summer,' with improved food and living conditions. In the second year, before the crossing was begun, the seasonal rise and fall was observed.

In all cases skin-fold thickness is highly correlated with weight change.

Fully to interpret these findings, energy expenditure and food intake need to be known. Much has been written on the effects of low environmental temperature on food intake. Although there are a good deal of contradictory data, majority opinion would hold that food intake increases as the temperature drops. Lewis and Masterton measured the food intake of four men individually during three separate periods, two at the base and the other on a sledging journey, totalling 108 man-days. At the same time energy expenditure was estimated from carefully kept diaries of activity.

Food intake and energy expenditure varied very considerably at the base, intake ranging from 1,800 to over 8,000 Cal. (kilocalories) in any one day, and expenditure from 2,200 to 6,000 Cal. The average was 3,800 Cal. intake and the expenditure was estimated at 3,600 Cal. During sledging, the intake rose to 4,740 Cal. and the expenditure averaged 5,160 Cal. The ranges of intake were relatively slight, from 4,000 to 5,500 Cal./day, although expenditure varied as there were days when weather prevented sledging and the range was 2,300 to 7,000 Cal. (9).

Lewis and Masterton also measured the fat content of the feces, as over 56% of all calories were obtained from fat during sledging. Over 96% of this fat was absorbed, and the fat content of the feces was within normal limits (9).

In the Antarctic, Rogers carried out a dietary survey on one man for a week during the winter. Intake averaged just over 4,000 Cal/day. The subject was a large man with a surface area of 2.14 sq.m. Rogers measured the energy expenditure with the Integrating Motor Pneumotachograph (I.M.P.), and the average figure was close to 4,000 Cal/day (personal communication from A. Rogers).

A number of estimates of food intake have been made at different Antarctic bases and during sledging. Goldsmith estimated the intake of two men during sledging and found it to be about 4,200 Cal/day. This is based on 70 man-days, consisting of three separate journeys under varying conditions. At the base, where as mentioned above conditions were severe, only a very rough estimate

FIG. 2. Card used for recording physiological data on the Trans-Antarctic Expedition at bases on the Antarctic Continent. Cards were completed at weekly or monthly intervals for clothing and weight records; duration of sleep was recorded daily on the right-hand part of the card.

of intake over the year could be made, but it was probably of the order of 3,300–3,700 Cal/day. On this intake there was a considerable weight loss, of the order of 3 kg, so energy expenditure may have been 3,500–3,900 Cal/day.

During the crossing of the Antarctic Continent there was a weight loss on the first part of the journey when there were great difficulties. From the South Pole onwards, conditions were much easier and, from fragmentary data, it seems there was little change in weight. Food intake can again only be tentatively estimated, but it appears to have been of the order of 4,500 Cal/day (A. Rogers, personal communication).

All of the figures for intake and expenditure are high, compared with surveys in Britain where an intake of 4,000 Cal/day is rarely found. Even very active subjects such as army recruits during training have an intake of 3,900 Cal. and an expenditure of 3,750 Cal/day. So the findings from polar expeditions would support the view that food intake is raised in the cold. But no information is yet available as to the reason for the high energy expenditure. The BMR is not raised, and measurements of oxygen intake during sleep confirm this. The energy expenditures recorded by Rogers appear to indicate larger expenditures than might have been predicted. But in general it seems probable that the high energy expenditure is simply due to a raised level of physical activity. Lewis and Masterton computed their energy expenditures from figures derived from studies in Britain, and their computations appeared to fit the intakes reasonably well. So energy expenditures on similar tasks are unlikely to be very different in cold environments from those in temperate climates. More direct measurements of energy expenditure are needed, however, as in some cases it is not easy to estimate the way in which energy is expended.

The changes in body weight with season are at present most plausibly explained on the basis of changes in energy expenditure, being lower in the winter than in the summer. But it is not an entirely satisfactory explanation, as man in general appears to regulate his calorie balance remarkably well whatever his energy expenditure. The regularity of the seasonal change suggests a possible biological rather than a sociological basis. Parallel studies also need to be done in temperate countries. It is perhaps worth mentioning that a special group of people can put on fat for insulating purposes. These are the long-distance swimmers, and the evidence suggests that they put on fat preferentially in subcutaneous areas rather than deep fat depots. It is possible that this may be in response to a cold stimulus, which is greater than experienced by most polar travelers, i.e. cold water with skin temperature down to 15°C (10).

If man does acclimatize to cold, then he might be expected to wear less clothing in a particular environment after sufficient time elapsed. On the card (fig. 2) on which records are kept, details of clothing are given and it has been possible to obtain complete clothing diaries for a period of a year. Two sets of data have been analyzed, one kept by Dr. Evans at Horseshoe Island and the other by Dr. Goldsmith at Shackleton Base (see fig 1). The variety of clothing worn was very considerable, and it was finally decided to use the simplest form of analysis, that is, to count the number of layers worn over hands, feet, lower and upper half of body, i.e. above and below the waistline. There was an adequate amount of clothing, and men dressed for comfort. As it got colder men wore more and discarded clothes as it became warmer. At Shackleton they wore less, however, in the spring and summer than they had done in the previous autumn, so days of similar weather were examined, when the wind chill was the same, at different seasons of the year. Comparing the first and last quarter of the year, fewer gloves and socks were worn and there was a small but not significant reduction in the amount of clothes worn over the body. However, in the latter part of the year clothes were worn and dirty, and their insulating value must have been reduced, although it is not known how much (11).

This difference was not observed at Horseshoe Island where temperatures averaged some 15°C warmer. This rather crude technique of evaluating clothing can obviously be elaborated and should be capable of giving useful information.

Skin temperatures have usually been measured in studies of acclimatization. It has not been easy to do this in the field without considerable interference with the activities of the subject. A new technique has been developed by Wolff (12) that consists of a resistance thermometer woven into a wire suit and worn under the clothing next to the skin. By this means the subclothing temperature can be recorded without interfering with the activities of the individual. Adam has studied three groups of subjects in the Antarctic, including members of the Trans-Antarctic Expedition at the end of their journey, some of the New Zealand party who had been sledging for many months, and several newcomers who had only been at Scott Base for 3 weeks or so. Temperatures were recorded under a variety of conditions, and sensations of comfort were also recorded. It might have been expected that the members of the Trans-Antarctic Expedition would have been fully acclimatized to cold, and one of the features of such acclimatization would be the ability to tolerate a low skin temperature with comfort. But, surprisingly, there were no differences between the three groups in the subclothing temperatures recorded and the comfort experienced (13).

Polar regions are not only cold: there is also the marked alternation of dark and light, with the long polar night and up to 24 hours daylight in the summer. There have been many accounts of the effect of such unusual patterns on man, but these accounts have in general been highly colored and inaccurate.

Lewis and Masterton decided to record sleep in Greenland, to find out if sleep patterns were disrupted. During 24 hours dark and light there was a marked alteration in the general pattern. But the total number of hours of sleep was remarkably constant throughout the

year and there was little difference between the seasons. Men could sleep as long as they wished, so it was interesting to find that the average worked out to be 7 hr. 59 min., perhaps justifying the assumption that we need 8 hours sleep a day. Further records have been made in parts of the Antarctic, and the average has come out to be close to 8 hours a day (14).

Although many useful observations on sleep have been made as a result of this intensive study, little has been learned about the effects of a polar environment. Rather, it has shown once again what admirable places the polar regions are for the study of fundamental human biology.

There have been a number of other studies made, including blood changes, blood levels of cholinesterase, frostbite, nail growth and hair growth, cold diuresis and water balance. Dr. Lobban has used Spitzbergen as an ideal laboratory for the study of diurnal rhythms (15). Dr. Massey has confirmed, in Antarctica, Mackworth's account of local acclimatization of hands to cold (16). There were two groups of subjects, newcomers and 2nd-year men. There was initially a highly significant difference between the two groups, which slowly diminished until there was no evident difference after 7–8 weeks.

What conclusions can be drawn from these observations? First, that there is need for more work, including continuation of body-weight and skin-fold measurements and clothing diaries. It is necessary to measure food intake systematically and to obtain as much information as possible on energy expenditure. But the outstanding question which must be answered before the problem of acclimatization can be adequately studied is to know to what degree of cold the subjects are exposed. Wolff has designed a temperature-sensitive watch which can be set to stop below a given temperature and to start again when the temperature rises above the set point (17). By using one watch, the time spent daily indoors and outdoors can easily be measured. It has already been successfully used by Goldsmith, who found one subject with an exposure outdoors of less than 1 hour in a month. In general, subjects considerably overestimate the time spent out-of-doors, and, except for serious accidents such as those which affected the 1st-year men of the Trans-Antarctic Expedition, in polar bases today the indoor temperature is quite high, very rarely below 12°C and frequently over 20°C. The difficulty is going to be to find men who are exposed to cold in any way comparable to the cold exposure used in the laboratory studies of small animals.

The second conclusion is that nothing discovered so far would upset a negative hypothesis: that is, that man does not adapt, physiologically, to cold. This might be stated in another way, as suggested by Macpherson (18), that man, tropical animal as he is, in moving to temperate climates has adapted to them and is already as fully acclimatized as he can be. He has already reached the limits of physiological adjustment and can go no further.

To put forward a negative hypothesis is not necessarily the same as saying that man does not and cannot adapt to cold. But the relatively complete failure to find any adaptation makes it more sensible to begin with a negative hypothesis and then try to demolish it.

What is against it? The changes observed include:

a) A seasonal increase in body weight and subcutaneous fat thickness during the polar winter. The most likely explanation at present is that this change is due to social rather than environmental factors.

b) Clothing records, which show clearly that less clothing is worn over the extremities after some months of exposure, and some evidence that such a change is not observed with mild cold exposure. Coupled with this is the evidence that sleep in severe cold gradually improves. Such changes, if they are accepted as real, do not necessarily indicate a physiological change, by which is meant alterations in the mechanisms of the body which can be measured objectively. The wearing of fewer clothes, and the ability to sleep in the cold, can be due to a changed response to sensory stimuli, which might be analogous to learning or habituation. The subject learns to ignore the sensory information from his skin telling him he is cold.

c) Local adaptation of hands and possibly feet. This still remains as the most unequivocal evidence of the physiological effects of cold on man. It has been confirmed by Massey and the observations on clothing also support this view. More work is needed to determine what the nature of the change in the hands may be.

d) Increased food intake and energy expenditure in the cold. The results described support this finding, but the most reasonable explanation is that energy expenditure is raised because the subjects are active. Until there is clear evidence to the contrary, it would be unwise to evoke a specific effect of cold on food consumption in man.

e) The final conclusion is that the most valuable aspects of polar physiology are not concerned with cold at all. Diurnal rhythms, sleep patterns, changes in the BMR, body weight and skin-fold thickness, these and many other phenomena can be studied more effectively in the Antarctic than in temperate regions.

REFERENCES

1. Mackworth, N. H. *J. Appl. Physiol.* 5: 533, 1953.
2. Scholander, P. F., H. T. Hammel, J. S. Hart, D. H. Le-Messurier and J. Steen. *J. Appl. Physiol.* 13: 211, 1958.
3. Wyndham, C. H. and J. F. Morrison. *J. Appl. Physiol.* 13: 219, 1958.
4. Edholm, O. G. *et al. Advancement of Sci.* 53: 411, 1957.
5. Lewis, H. E. and J. P. Masterton. *Lancet* ii: 494, 1955.
6. Wilson, O. *Metabolism* 5: 453, 549, 1956.
7. Rosenbaum, S. *J. R. Statist. Soc., Lond. Ser. A* 117: Pt. iii, 1954.
8. Goldsmith, R. *Lancet* i: 741, 1959.
9. Masterton, J. P., H. E. Lewis and Elsie M. Widdowson. *Brit. J. Nutr.* 11: 346, 1947.

10. Pugh, L. G. C. E. and O. G. Edholm. *Lancet* ii: 761, 1955.
11. Goldsmith, R. *J. Physiol.* 148: 1959. In Press.
12. Wolff, H. S. *J. Physiol.* 142: 1P, 1958.
13. Adam, J. M. *J. Physiol.* 145: 26P, 1959.
14. Lewis, H. E. and J. P. Masterton. *Lancet* i: 1262, 1957.
15. Lewis, P. R. and Mary C. Lobban. *Quart. J. Exper. Physiol.* 42: 356, 1957.
16. Massey, P. M. O. *J. Appl. Physiol.* 14: 616, 1959.
17. Wolff, H. S. *J. Physiol.* 147: 35P, 1959.
18. Macpherson, R. K. *Nature, London* 182: 1240, 1958.

Discussion

P. F. SCHOLANDER
Scripps Institution of Oceanography, La Jolla, California

Weary from all this cold talk, Dr. Edholm and I sat down over a glass and decided that we had better rig this evening's session like a wrestling match, with hero and villain, no holds barred, moaning and groaning, battle royal in the end, and nobody hurt, for where lies the real issue? So then, when the hero just claimed that man is no rat, my reply is this: He most certainly is, and a swine, too. And as to the notion that man does not acclimate to cold—also, this is for the birds.

Let us first briefly recall some of the basic ideas and findings that have been derived from animal studies, including man's close allies, rats and swine. We have seen that most of the larger arctic animals are so well insulated that they rest on the snow without any metabolic compensation at all. It has been shown also that the basal or resting heat production is the same in most tropical and arctic animals and men, in the sense that they all stay right on the well-known mouse-to-elephant curve. In general, therefore, the basal heat production gives little or no clue as to cold acclimation.

A great deal of work has been done by studying the metabolic and insulative response in animals when subjected to cold. It holds in general that the animals stay near basal until the critical temperature is reached. From then on they compensate metabolically, and their heat production follows essentially Newton's law of cooling. It is customary in these experiments simply to put the animal in a box and to lower the temperature in steps and then see what happens to the metabolic rate. There is no control over what the animal is doing, whether it curls up and shivers or thrashes about. Once in such an experiment, a fox dug himself almost through the metabolic cage.

Nevertheless, out of this sort of experiment come rather striking curves. Sometimes, as in Dr. Irving's winter experiments on rats from the city dump in Fairbanks, the animals manage to compensate against cold by raising the metabolic rate 5–6 times, and rather nicely in proportion to the body-to-air temperature gradient. But man at his normal wits simply will not take such treatments, and even a night of +20°C is quite bad for naked man; if you go only a little lower, he becomes seriously chilled unless you allow him to do exercise. If you put him on a bicycle-ergometer and ask him to exercise enough so that he neither sweats nor gets goose pimples, he will about quadruple his heat production at 0°C, which corresponds to a critical temperature of about 27°C. But without exercise he can hardly double his heat production for any sustained time.

However, many little birds in the northern forests who do not seek protection by shelter have a critical temperature of between +10° and +20°C, and must for prolonged times, day and night, triple or more their metabolic heat production. This they do by shivering, and it has also been observed that this shivering is compatible with rest and sleep. In the daytime there is no particular problem, because then they can and must move about in order to 'refuel,' but at night they must rest and sleep and must furnish the heat by other means than locomotion.

Rest and sleep in higher vertebrates is such a fundamental function that unless the animal is able to do this, we cannot consider him acclimated to the environment; and this is a point which is equally important for man.

Those among you have been out in an emergency situation, especially in the wintertime, will know by experience that the night is the toughest time. Sooner or later you must be able to lie down and rest, and unless you can do this without dying from exposure, you certainly are not adapted to the environment. If, now, as a result of exposure, changes take place in you which enable you to rest and sleep in the cold, which formerly you could not do, we have good justification for describing these changes as adaptive to cold.

One would certainly expect that humans, like most other tropical animals of very high critical temperature, would be very limited in their capability of cold acclimation. Naked man could improve his insulation only very little by increasing his normal cold vasoconstriction, and one would also expect the metabolic response to be very modest in a sleeping man, even when acclimated. The point, therefore, would be to design a test where unacclimated man, during the nighttime, would be subjected to a moderate cold stress, just annoying enough to keep him awake. In most subjects spending a night naked at +20°C has this quality, especially in the early morning, but a better test is obtained by putting a naked man in a single-blanket sleeping bag at around 0°C. The over-all cold stress in this procedure is about the same as before, in the sense that it requires an increase of metabolic rate of some 30–50% in order to maintain thermal balance. But it has the advantage that circulatory changes show up better. If, for instance, the feet are poorly circulated, the skin temperature may readily go below the pain threshold of some 15°C, which of course it cannot do in a 20° room. Furthermore, at least white man likes to be covered at night. Sleep or no sleep merely serves as a convenient clue as to what has taken place, and it also fits well the requirement that prolonged tests be used because heat capacity of man is so much greater than his heat production. A cardinal point is to

not drown out by too severe a stress whatever small compensation the man can muster.

Now, one reason why we undertook a study of this sort was the provocative idea held by my esteemed adversary, namely, that man is incapable of acclimating to cold. This goes so strongly against common experience that it called for action. For who has not experienced while camping that something happens to enable you to sleep comfortably where the cold kept you awake before? I think this is a point which might be somewhat difficult for a Britisher to grasp fully, because I have never in my life frozen so badly as I did in the hyper-British hotel in Adelaide in Australia, where we spent a week without heating. One need not necessarily study the general problem of cold acclimation in the polar regions, for you can easily get as much chilling as you wish by sitting naked in this lecture room. I might say that if a particular set of physiological tests fail to prove a common experience, we had better chuck the tests rather than the experience.

Here, then, we found ourselves provoked to try to find out what takes place under camping conditions. A group of students went hiking, fishing and reindeer shooting in September and October in the Norwegian mountains above tree line, wearing in the daytime mostly summer clothing, but spending the night under controlled conditions. Each student received a single-layer sleeping bag made out of one military blanket. This was furnished with a thin wind cover, and into this assembly they stepped essentially naked. You may more or less instinctively feel that this is not a very warm rig to sleep in when the ground is covered with frost, sleet or snow. Reaction to this differs somewhat in different persons, but most of us find it rather bad, especially when the feet chill so much that we cannot possibly sleep. Now these boys did this for 6 weeks and reported back that already in the course of about 1 week the symptoms of chill and wakefulness left them. They observed that a man could be lying there, snoring and shivering in his bag, and it would take quite a jolt for his side man to wake him up. You see how we are getting closer to the rat by the minute!

The most conspicuous change that had taken place in these men was that the feet, instead of cooling more and more, now stayed mostly above 30°C all night; this, of course, at the cost of an increased metabolic rate. So in this change of peripheral circulation we have an objective demonstration that something happened to these guys which made it possible for them to find rest in their environment. This vascular adjustment one may certainly term a natural adaptation to cold, for the men met the situation by a natural behavior, being normally active in the daytime and seeking rest at night. To what extent the amount and quality of food and exercise would influence this general reaction is a different matter. Naturally, maintenance of warm skin temperature all over occurs at the cost of an increased metabolic rate, and a similar increase in metabolic rate was also maintained by the control persons in their thrashing about and shivering all night. Some of the boys stepped up their night metabolic rate by 75%-90% and still found a sleepful rest, and some of them found that they were unable to keep on a normal amount of bed clothing in the weeks following the exposure. So far, therefore, this is similar to what has been observed, especially in little birds, for also they compensate against the cold by increased heat production during sleep.

Two notions of metabolic acclimation are currently in use. According to the first, it simply means that the observed, improved fitness to cold (e.g. evidenced by sleep) is effected by elevating the heat production above the resting level. This stands in simple and logical contrast to acclimation by improved insulation. Other students prefer a somewhat narrower definition, namely, that some quantitative and qualitative change in the process of heat production should also be involved, such as is well known to occur in the cold-acclimated rat. It is to be hoped that some day other animals will be observed equally well.

Now another, to me, obvious reason for concluding that man is able to acclimate to cold comes from a study of naked human races. With the critical temperature of naked man of about +27°C, over-all cooling becomes a much more acute problem to naked man in the tropics than to fur-clad man in the Arctic. People like the Tierra del Fuegan Indians, living naked in a climate which even in the summertime might produce snow showers, must surely have been different from ourselves. They ate sea food and often swam in the icy waters. We hope to find some remnants of these people in the next few months and hope to learn something of their physiology.

Other naked peoples studied are the Australian aboriginals, who were studied some 25 years ago by Sir Stanton Hicks of the University of Adelaide. He made several expeditions to central Australia at the time when the aboriginals were still living completely naked in the desert, sleeping on the ground at night with recorded temperatures as low as −8°C, protected from the weather only by little windbreaks, and typically lying between two or three little fires. He found that these people would allow themselves to cool down considerably more than we do; +12°C foot temperature was not uncommon. He also did metabolic studies and found that the aboriginals did not compensate metabolically against the cold of the early morning.

Even though the natives had been wearing clothing for the last ten years or so, we still thought it worthwhile to try to get some further information out of them. So on our Australian winter and summer expeditions we repeated and confirmed Hicks' results, and in addition we put the aboriginals through the bag test we had used in Norway.

It turned out that on a windless night one could easily derive sufficient heat from the little camp fires to sustain heat balance, but on windy nights this was a very rough deal. The situation was closely analyzed by Dr. Hammel, who found that the thermal conditions between the scorching fires and the cold night sky could not possibly be quantified. This, then, called for the bag test which we had been using before. It does not require much imagination to realize that the least attractive part of our task was to approach a young warrior with a rectal thermometer, and the first night, under a glorious Milky Way and in the dim light of the camp fires, the immediate reaction of the young man was to bolt out into the darkness, thermocouple leads attached, but luckily leaving the instruments behind. It turned out that the natives cooled even more on their feet than we did, but whereas this kept us awake, the natives were snoring through the whole situation. Hammel, on the second expedition, showed that the Central Australian natives reacted the same in the summer as in the winter, but the tropical North Australian natives reacted more like ourselves. This implies genetic factors in human cold acclimation.

When Irving studied the reaction of Alaska swine to cold, he found a striking skin cooling in these naked animals, and whereas the aboriginal may well share his skin cooling with the swine, we uphold this relation better in most other respects.

It seems, therefore, that one may distinguish between two clear types of general acclimation in man. One is the type presented by the Norwegian students with improved peripheral circulation and increased metabolic rate. The second is the opposite, so to speak, found in the Australian aboriginals with

XUM

insulative cooling of their body surface and lack of metabolic response. These two modes of adaptation fit well with what is known about acclimation in rats and swine and little birds.

I should like to make a few comments here—although there are other people in this audience who know this subject better than I do—about the situation in arctic people. The crucial question which must be asked here is: to what extent are these people subjected to cooling? Here we are up against a difficult situation, because it seems to me that no matter how much thermometry we apply inside their clothing, we are never going to know the whole situation. We are at most going to be able to integrate a certain situation. You need a score of thermometer-clocks going all the time, and these must be worn inside, not outside the clothing. The few temperature measurements which have been made inside the clothing of Lapps showed no difference from our own standards, and some of you undoubtedly will have experienced that Eskimo clothing is warm also for white man.

It seems, nevertheless, likely that cold acclimation in these people can develop temporarily as a result of hardships on hunting trips, or seasonally. Even if physiologists do not happen to catch it at the right time, one should not entirely neglect the experience and impressions of northern travelers in this respect. I believe that the only reason for disagreement on acclimation data on man goes back to semantics or the nature of definitions. But I personally do see a great connection between what we know about animal acclimation and what we know about human acclimation.

Commentary on antarctic operations[1]

PAUL SIPLE
Scientific Adviser, Army Research Office, Washington, D.C.

I WOULD never have gotten up to talk on acclimation in this august company without an invitation. I belong on the side of the subjective reactor in this field of study, if there is such a thing as cold acclimation.

I have watched groups of men exposed to cold and have seen that something occurs in about 2 weeks; whether it is a physiological or psychological reaction, or both, is difficult to say. Two of our men went out voluntarily to see just how long they could stay at a temperature of −98°F with a wind velocity of fifteen miles. They were dressed in the equivalent of three layers of clothing and were able to stay out for 3 and 4 hours. Other men stayed outside for 2 hours at −100°F. Nonvoluntary exposure, combined with work, occurred in the snow mines at −60°F where men were digging tunnels 90 feet below the surface. Some men, including myself, could work as long as 4 hours; however, the usual duration was 1 or 2 hours. This seemed to be the limit of physiological capability as some men developed labored breathing and bleeding in the bronchial tract.

The problem of cold was complicated by the fact that the camp was at 9,000 feet; outdoor work at −90°F and 9,000 feet affected the men as much as it had at −60°F and sea level. Further analysis led to the conclusion that the thermocapacity of air was less at high elevations than at sea level; −90°F at 9,000 feet was found equivalent to −60° to −70°F at sea level.

The problem of adaptation to cold included learning to recognize the sensation of freezing. The winds at −90°F and 9,000 feet were usually about 15 knots; the freezing time for ears, nose and cheeks was about 45 seconds. The men who had been in the cold longest recognized the sensation of freezing immediately; the new men often suffered more from frostbite.

Men who had been at the station for some time did not appreciate the part their adaptation to the temperature and elevation played in their ability to work and be comfortable until new men joined the group. There was little opportunity for newcomers to adjust to the environment before going to work; these men usually became exhausted immediately while performing the lightest tasks. During their year of residence, however, the men adapted sufficiently to handle 400-lb. fuel drums and other heavy cargo for 4 hours at temperatures of −45°F or lower at the altitude of 9,000 feet.

Loss of weight during this stress was as high as 10% to 16% of body weight within a period of a few weeks to a couple of months. Many of the men also suffered from rheumatism–like pains in the elbows, knuckles and shoulders. The physiological adaptation often reached a limit with ensuing loss of strength and general physical debilitation. I feel sure that man's adjustment to cold includes psychological as well as physiological factors.

[1] Condensed from a recorded extemporaneous talk by Dr. Siple.

Discussion

O. G. EDHOLM, P. F. SCHOLANDER, J. S. HART, L. D. CARLSON, L. IRVING

DR. EDHOLM: I think we are still in the state in which we came in. My head is bloody and a little bowed. We have not yet been able to agree as to what we are going to consider evidence for adaptation. Therefore I would like to pose some questions. There is the mass of evidence from animal work: all animals which have been carefully examined in the laboratory do show adaptation to the cold in the sense that they undergo measurable physiological changes that make them more successful in withstanding cold stress. How much cold exposure is needed to produce such changes in man? We have seen what the Norwegian students were able to do when exposed to cold stress. I think there is some evidence for adaptation in the Channel swimmers exposed to cold water at 15°C for long periods; they appear to adapt by selectively putting on fat in their subcutaneous tissue.

Some years ago, Dr. Bazett suggested that men living in tropical countries should be brought to cold places and their adaptation studied. Perhaps man living in the British climate, as Dr. Scholander has already indicated, is severely exposed to cold and already fully adapted. It would therefore be more sensible to take people from the tropics to Britain or other cold countries and study them in detail. This has not yet been done. The work of Dr. Scholander and his colleagues on men living in cold conditions has shown that man can learn to sleep when he is cold. We also have evidence that local acclimatization to cold can be developed in the extremities; I think there is clear evidence of small but useful vascular changes in the hands. Mackworth first demonstrated cold adaptation in the hands when he compared indoor and outdoor workers at Fort Churchill. There could have been a difference in the amount of use of the hands in these two groups. He then continued his study in a cold chamber at Cambridge, with his subjects sitting for 2 hours daily at a low temperature. Adaptation to cold in the hands was demonstrated after some 2 weeks of daily exposure and increased during subsequent weeks in the cold chamber. In this experiment, the factor of manual work in the cold was eliminated. I would therefore accept the view that local adaptation to cold can be demonstrated in the hands and probably the feet. The fact that men can learn to sleep in the cold may not necessarily be evidence of acclimatization to cold, only that man can learn to ignore sensations from the skin. Subjects unaccustomed to sleeping on a hard floor sleep badly at first, but after a few days or weeks sleep soundly. To come back to the problem of a definition of acclimatization, I want to have evidence of measurable physiological changes in man before I accept his adaptation to cold.

DR. SCHOLANDER: When a condition of no sleep changes into one of sleep, it is subjectively quite a dramatic clue that some change must have taken place; this is even more significant when it can be shown to be correlated with measurable physiological phenomena, such as warm extremities and a very marked elevation in sleeping heat production. One may mention also shivering during sleep. We got some evidence from electroencephalography that in man mild sleep is compatible with shivering, which we already know is true in rats. I think that even better evidence of this was obtained in the Old Crow experiments on Indians by Irving's party. But there are certainly other than psychological factors involved. The improvement of leg circulation, for instance, is a very striking change, and I cannot see any sense in subtracting the extremities from the general picture.

DR. HART: It is apparent that the evidence for cold acclimation points to peripheral adjustments in the feet and in the hands (i.e. warmer extremities), a subjective change in reaction to cold, and better ability to sleep. However, I draw the line there insofar as resemblance to the rat is concerned. When acclimated to cold the rat does resemble man in peripheral adjustments, but for human systemic adjustments, or metabolic acclimation as Dr Scholander has termed it I think there is absolutely no evidence whatsoever. It it still necessary to demonstrate the ability of cold-acclimated man either to maintain a higher heat production for some limited period of time, or to elevate his heat production to a greater extent than unacclimated man. The data that we have seen so far do not show this at all, and I think that is the point where the disagreement arises.

DR. CARLSON: I would like to say, for Dr. Edholm's defense, that I can remember Dr. Scholander remarking to me, "Carlson, there is no such thing as adaptation in man," and furthermore, he defined adaptation to me as a change which must be in the direction of a minimal energy output. We had a long discussion on this, because at the time I had just spent 2 or 3 weeks of the winter in the Arctic trying to expose myself and five others to the cold. There are many things that will have to be considered with respect to adaptation in man. One is that I think we are neglecting much of the early work: Bruno Balke's (1) first demonstration of the shift in the hand temperatures, for example, or Bazett's (2) and Adolph's (3) work which gave the first indications concerning adaptation in the cold. I think there is still some merit in the hypothesis we (4) put forth that there is a change in the core and shell relationship because it has now been confirmed, at least by inference, from Rennie's (5) and Elsner's (6) work. This, however, can only be confirmed by doing complete direct and indirect calorimetry, since a balance is necessary in order to make these statements. One of the real problems in comparing man with a rat is that the man has a large heat content in proportion to the rat. You have to expose the subject in such a manner as to take this into account. I would like to mention that Bass has accomplished an excellent experiment in having people live at 10°C for two weeks at Natick Laboratory and has shown some things which are comparable to the rat. Finally, attention should be directed to physical fitnesss and adaptation as in Tom Adams' (7) work: Adams gets some comparable results in terms of the peripheral circulation that are brought about by physically training people, so that there is an actual carry-over from training to the response to cold.

DR. IRVING: I disagree heartily with Sandy Hart's disagreement, for I consider the evidence quite satisfactory that the Australians showed an adaptation when they let their feet and, less markedly, their bodies cool without any perceptible metabolic elevation. That shows the conservative economy of their adaptation. I am not so certain that the expensive evolution of extra heat to preserve warmth appears quite as satisfactory as

adaptation. Hart, Steen and others have recently clearly demonstrated that in their cold natural habitat small birds and small mammals must always expend no less than two or three times the basal production of metabolic heat. I must grant that, although uneconomical in appearance, this remarkable faculty is nevertheless a satisfactory adaptive process because it appears in normal populations.

I think that one of the difficulties in these debates about defining adaptation is that we frequently try to give a special physiological meaning to common words in the English language; we cannot pervert them to our temporary physiological inclination without getting into trouble. I think that Dr. Scholander's description of adaptation is satisfactory because it is about what you would find in the dictionary. Much of the difficulty in defining the significance of our various observations, however, comes from the failure to realize that biologically adaptation is related to the fitness of a race or a population of animals. In its biological connotation it is not related so much to the individual as to a characteristic which permits a race or a population to exist. Now as to whether rats are a race —white rats, anyway—or whether they are a population living in their man-provided warmth, they are not to be compared with natural populations which survive or perish by the degree of their adaptation to cold. What makes the demonstrations of human adaptation to cold interesting is the fact that natural human populations have been chosen for the subjects, and a natural human population is just what it means and is likely to be: regular, reliable and homogeneous.

The only counterpart to experimenting with natural populations is working with trained people, for with untrained people, as we know, erratic results are certain. So there again the choice of young fellows, who were motivated eagerly to accept training in exposure, gave the young Norwegians on Hardangervidda a clear case of adaptation; if you force some poor soldiers into the cold room, the training is usually not very successful. Neither are students highly motivated to exertion by any rewarding experience from sitting in a cold room.

Somebody remarked that ignoring sensations of cold may go along with the improved tolerance to cold by the Australian aborigines. I do not see how it is possible to think that a valuable adaptation could depend upon numbness or insensitivity of tissues. In fact, recently some young fellows who for religious reasons go barefooted in Alaska could remain in a cold room until their toes were as cold as 5°, 6°, and 7° for as long as 45 minutes. During that time they were not at all insensitive; there was no pain, but they informed me several times of local warming reactions which involved changes of only the order of a tenth of a degree. So actually the sensitivity, perception, and awareness and monitoring of their own heat condition was quite superior in these people who were trained to exposure.

REFERENCES

1. Balke, B., H. D. Cremer, K. Kramer and R. Reichel. *Klin. Wchnschr.* 23: 204, 1944.
2. Bazett, H. C., F. W. Sunderman, J. Doupe and J. C. Scott. *Am. J. Physiol.* 129: 69, 1940.
3. Adolph, E. F. and G. Molnar. *Am. J. Physiol.* 146: 507, 1946.
4. Carlson, L. D. *Man In Cold Environment.* Arctic Aeromedical Laboratory, Ladd Air Force Base, 1954.
5. Rennie, D. W. In: *Cold Injury*, edited by I. Ferrer. New York: Macy, 1958, p. 253.
6. Elsner, R. W. Arctic Aeromedical Laboratory Project #8-7951, Rept. No. 1, 1955.
7. Adams, T. and E. J. Heberling. *J. Appl. Physiol.* 13: 226, 1958.

Man in a cold environment

Summary

LAURENCE IRVING

Arctic Health Research Center, Anchorage, Alaska

Drs. Edholm and Siple have vividly described conditions in antarctic camps where men of various origins and experience were engaged in work ranging from sedentary housekeeping in winter to strenuous unloading, construction and trail parties in summer. In one camp annual activity was estimated from food consumption to vary from 3,900 Cal. daily in winter to 4,900 in summer. The winter food exceeded needs, judged by common gain in weight. In summer average weight diminished and in trail parties the loss in weight indicated some days of work expended 6,000 Cal. These were averages obtained from extremely diverse estimates of individual activity and exposure.

Basal metabolic rates have been extensively recorded in the Antarctic, as in every situation where a physician or physiologist can set up his apparatus. The consensus of recent and earlier observations in the Antarctic often showed a little fall of BMR in winter and a small summer rise that was scarcely statistically significant and not visibly adaptive. Long ago Lindhard remarked a small decrease in his BMR in Greenland along with gain in weight during the depression of an inactive winter, and

some loss of weight and suggestion of an increase in BMR with returning vigor during the active summer. Evidently there are large variations in the exposure and activities of an expeditionary population which are not reflected in changing basal metabolic rates.

Small variations in metabolic rate and regular changes in body temperature may appear in any situation according to a diurnal rhythm. For a given short time in the day and with fair technique a 20% deviation from the average in metabolic rate or 0.3°C departure from average in body temperature suggests abnormality and and suspicion of disease if confirmed by repeated tests and verification of measurements. It is difficult to gain assurance of the technical reliability of metabolic measurements made under the difficulties of conditions in the field. To my mind the reports are obscured by the common reference of respiratory measurements to surface area of the body calculated from a few measurements of body size with numerical factors which are constants of convention.

The classical measurements of Benedict and Dubois showed that a healthy man's BMR under standard conditions is a characteristic changing only slowly with age. The metabolic rate of man varies with size. Among animals from the size of a mouse to an elephant the BMR varies in better relation to size than to any external conditions or internal characters. There are deviations among species which are perhaps referable to taxonomic groups, and there may be small departures from the size relation with activity and diet. Viewing the human species comparatively, the normal BMR found in the extraordinary diversity of subjects, conditions and methods in the Antarctic adds evidence that the BMR is a size-related specific character which is not adaptable to external conditions. It has apparently been fixed during the long course of evolution from the origins of mammalian warm-blooded metabolism.

Experimentation of civilized physiologists is limited by the complaints of urban man against a little cooling of any part of his body. We can expose a rat to large thermal changes without consulting its feelings. Norway rats from an Alaska city made a much more powerful metabolic reaction to cold than laboratory white rats and the wild rat sustained its body temperature in air much colder than could be tolerated by a white rat of the same size and pelage. By activity or other means of thermogenesis, wild arctic animals can long maintain body temperature in air much colder than their critical temperature. As was remarked, men differ in size from rats but their metabolic reaction to cold seems to be somewhat inferior to that of the white rat. Both seem to show the result of shelter from cold.

It was also remarked that men resemble swine, at least in size and hairlessness. Swine show comfort and discomfort so plainly that I can safely say that a naked Alaskan hog can be comfortable in air at −20°C when its skin measures colder than 10°C. Evidently the cold skin represents insulation, for the critical temperature of 50 kg pigs is about 0°C. For man with warm skin the critical temperature is 27°C. Although an inactive man makes a comparatively poor metabolic reaction to cold, if he can generate heat by cycling, the increase of heat production in air colder than the critical temperature is in linear relation to the air temperature, as is the rule for wild arctic mammals.

Adaptation to cold is clearly demonstrable among arctic animals over large ranges of heat and temperature. In comparison it is hard to demonstrate physiological adaptation to cold in man. But the great adaptation of arctic animals to cold was demonstrated in contrast to tropical animals in which adaptation, although small, was nevertheless real and important. When Scholander and I expressed opinions that the adaptation of man to cold was not significant we were impressed by its modest limits compared with those seen in the insulative adaptation of arctic animals. I have no compunction about correcting that view now by saying that comparative physiological methods demonstrate significant and important human adaptation.

In order to demonstrate human adaptation to cold it has been necessary to consider men as we regard animal populations, which we physiologists have been reluctant to do except in bad humor. Like man, a white rat is not an easy subject in which to demonstrate adaptation because its thermal dimensions are small. Exposed to an overload of cold, thermal regulation disintegrates in man and white rats like any physiological regulation subjected to unusual and excessive stress. Practice is involved in the clear expression of physiological function. For training to be effective it must evoke exertion which in turn involves motivation. Soldiers and students thrust into a cold room are rather bored than trained by the situation. But the young Norwegians in scant clothing on chilly Hardangervidda enjoyed freedom of life on the high moors away from university routine and soon became able to rest at night by increasing their expenditure of metabolic heat to keep tolerably warm. This was adaptive in the sense of being a useful physiological adjustment.

This example of adaptation led Scholander to consider the reactions to cold of natural populations of men trained by living in a chilly climate. I completely agree that ability to rest is a good criterion of the success of an adaptive adjustment. The physiological reaction of Australian aborigines appeared in their ability to sleep with cold skin and economical maintenance of a resting metabolic rate. Natural populations of Lapps and of Yukon and Chilean Indians have shown various characteristic reactions to cold in which they differ from urban people. The reactions of these populations are commonly homogeneous, in contrast to the often erratic reactions of us urban folks of mixed ancestry and diverse experience. As a whole, or in part, some reactions of natural populations appear adaptive to their way of living. The thermal reactions of distinct populations of the human species fall into a much greater range and variety of patterns than could have been suspected from

studying the genetic and environmental mélange of urban societies.

I have no brief in defense of psychology but I think it an evasion to attribute to psychological conditions subjectively noticeable adaptability to cold for which we have not devised physiological demonstrations. Cold and its reactions are real and even in our sheltered existence cold is our commonest complaint about the environment. That animals or people can be adapted by insensitivity is impossible, for, in a frequent and dangerous natural condition like cold, a tissue that was insensitive would be both useless and doomed. I have found some people, in a cult accustomed to going barefoot, who tolerate very cold feet without pain while their toes were extremely sensitive to spontaneous local warming and cooling. And arctic birds and mammals are as sure-footed on their nearly ice-cold feet as the birds on the warm desert.

Edholm's wise comment suggested that we should address studies to tropical populations which may show as obvious minima the nature of adaptation to cold. Scholander indicated that he plans to make observations on islands in tropical seas. Now that his careful plans have been implemented, we can look forward to learning physiological secrets that are hidden by the thick clothing and chilly manners of frigid northerners.

I cannot imagine that we will ever find more gracious hosts than we have had in Buenos Aires at the Instituto Antartico Argentino. We owe thanks to the director for an environment in which the heat of debate has annealed the bond of friendly regard that joins us in the study of adaptation to cold.

II

Thermogenesis in the Acclimated Animal

Chairman: LAURENCE IRVING

Energy metabolism during exposure to cold[1]

J. S. HART
Division of Applied Biology, National Research Council, Ottawa, Canada

HART, J. S. *Energy metabolism during exposure to cold.* Fed. Proc. 19, Suppl. No. 5: 15–19. 1960.—Exposure of small mammals and birds to constant cold which results in chronic elevation of energy metabolism leads to well-defined alterations in metabolic processes. The most important of these is the development of an enhanced capability to elevate metabolism and maintain it at a high level and by this means to prolong survival at low lethal temperatures. Other associated changes include a gradual disappearance of shivering, an increase in peripheral temperatures (rats) and a decrease in body insulation (most species). Rats and deer mice exposed outdoors during summer and winter also have comparable changes in cold resistance and metabolic capability but differ in having increased pelage insulation (rats and mice) and lower peripheral temperatures (rats) during the cold season. It is concluded that seasonal and temperature-induced changes are not identical in these animals.

THE PHYSIOLOGY OF COLD EXPOSURE has become a subject of great importance in such diversified fields as comparative physiology and cellular biochemistry; the study of energy metabolism has occupied a central role in integrating ideas from these various fields. For those interested in the manner in which cellular energy exchange is regulated, cold as a tool is unique, since it is the only stimulus capable of evoking a chronic elevation of energy exchange. A short description will be given of the information available, both for chronic exposure of animals to cold in the laboratory and for exposure to cold in nature. For this description, the term 'acclimation' will be restricted to the effects of exposure to chronic cold where this is the only factor being changed, while 'acclimatization' will be used to describe seasonal changes in which multiple environmental effects are involved, i.e. where temperature is not the only variable factor.

[1] Contribution from the Division of Applied Biology, National Research Council, Ottawa, Canada; issued as N.R.C. No. 5956.

ACCLIMATION TO COLD

Acclimation to cold has been demonstrated by Blair (1), Sellers (2) and Hart (3), who found that chronic exposure led to a marked increase in ability to survive at temperatures that were ultimately lethal.

The energetics of this phenomenon were clarified when the oxygen consumption of deer mice acclimated to 10°, 20° and 30°C (4) was measured at −11°C and −20°C (fig. 1). Mice acclimated to 30°C, while showing an initial O_2 consumption equal to those acclimated to 20°C and 10°C, soon showed a fall in O_2 consumption and died. Those acclimated to 20°C maintained a high O_2 uptake for a longer period but ultimately succumbed. Mice acclimated to 10°C maintained a high metabolism

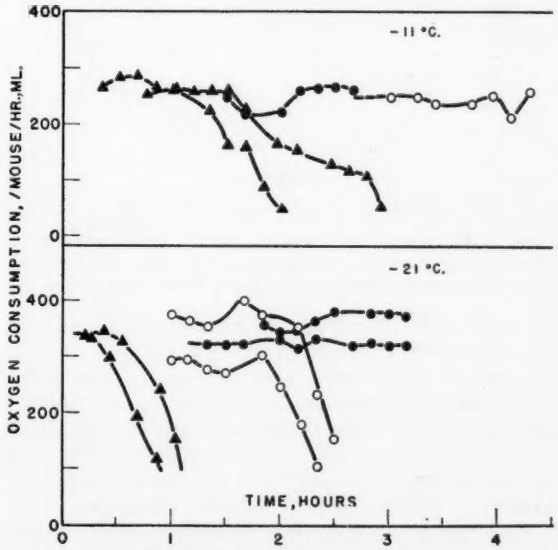


FIG. 1. O_2 consumption in single deer mice acclimated to 10°C (*solid circles*), 20°C (*open circles*) and 30°C (*triangles*) in relation to duration of exposure to −11°C and −21°C. From Hart (3).

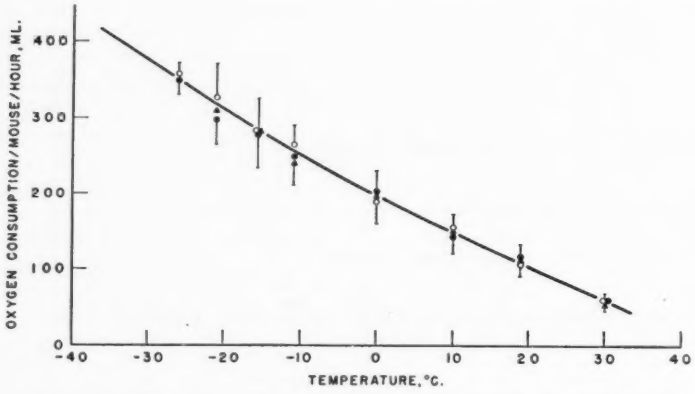


FIG. 2. Average O_2 consumption of mice acclimated to 10°C (*solid circles*), 20°C (*open circles*) and 30°C (*triangles*) at different environmental temperatures. Vertical bars give range. From Hart (3).

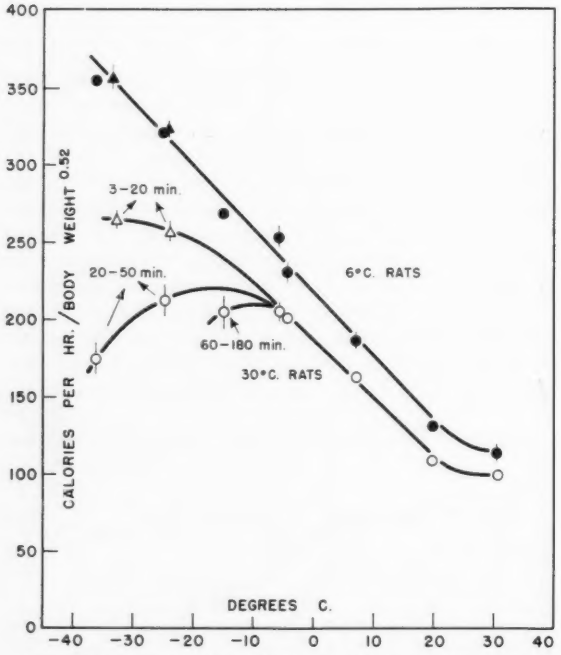


FIG. 3. Heat production of 30°C- and 6°C-acclimated rats for different intervals of time during exposure at various temperatures. Vertical bars are standard errors of mean. From Depocas *et al.* (8).

for the duration of the test. When the O_2 consumption was examined at different temperatures (fig. 2), absolutely no differences were observed. The cold-acclimated mice, however, were able to respire at higher rates and hence at lower temperatures than intermediate- or warm-acclimated mice. Therefore, the difference in survival at lethal temperatures can be accounted for entirely by differences in metabolic capabilities.

Examination of the temperature-metabolism curves (fig. 3) for the white rat (5) reveals an additional phenomenon not seen for deer mice; viz. that the heat production at 30°C as well as that at any lower temperature is greater for cold-acclimated animals. Since the curve for cold-acclimated rats is higher than and parallel to that for warm-acclimated rats, the additional heat produced cannot be considered as contributing to the capability of the organism to increase heat production (cold thermogenesis) in response to a cold environment. It is an energy cost of acclimation that does not aid directly in survival in the cold, but does aid in maintaining the periphery at a warmer level (6, 7).

Survival in the cold can be related to the ability of the rat to raise heat production from the thermoneutral level. A measure of this ability is given by the peak

TABLE 1. *Critical temperatures and Relative Metabolic Rates and Over-all Insulation in Mammals and Birds Acclimated to Warm* and Cold Environments*

Species	Author	Acclimation °C.	Critical Temp. °C.	Resting metabolism	Insulation
Dog	Gelineo	— 4° to + 5	25	134	75
		25°	25	100	100
Rabbit	"	— 6° to + 9	17	133	75
		29 — 32	17	100	100
Rat	"	0 — 2	32	158	64
		30 — 32	32	100	100
W. Rat	Cottle and Carlson	5°	25	100	100
		25°	25	100	100
" "	Krog and Irving	5°	23	145	69
		30°	23	100	100
" "	Sellers	1.5	30	150	67
		room temp.	30	100	100
" "	Depocas et al.	6	25	120	83
		30	**25**	100	100
Spermophile	Gelineo	29 — 32	30	190	53
		18 — 23	30	100	100
Fat dormouse	Kayser	8	28	138	72
		28	28	100	100
Dormouse	"	8	28	114	**88**
		20	28	100	100
Deer mouse	Hart	10	30	100	100
		30	30	100	100
Pigeons	Gelineo	— 1 to 3	25	129	78
		29 — 32	25	100	100
Doves	"	10 — 18	31	133	75
		29 — 32	31	100	100
Siskins	"	— 3 to 10	35	133	48
		29 — 32	31	100	100
Bramblings	"	— 14 to — 4	20	126	80
		14 — 18	20	100	100
Greenfinches	"	0 — 10	30	167	72
		29 — 32	32	100	100

* Warm = 100. From Hart (9).

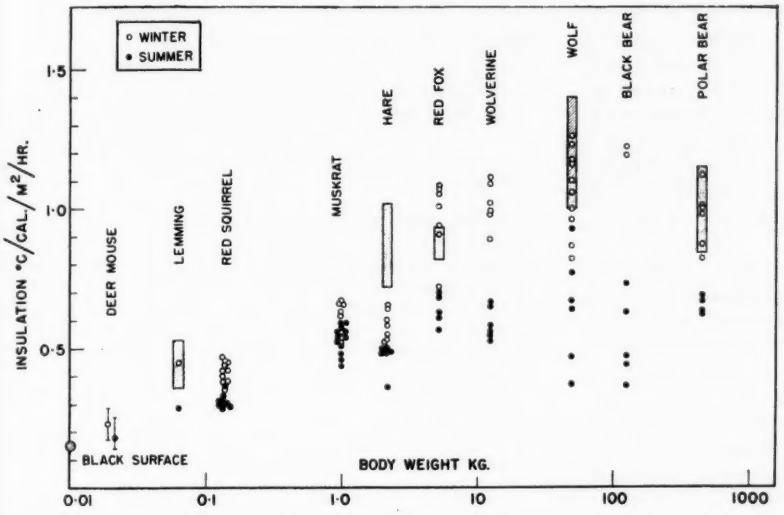


FIG. 4. Seasonal changes in fur insulation. From Hart (17).

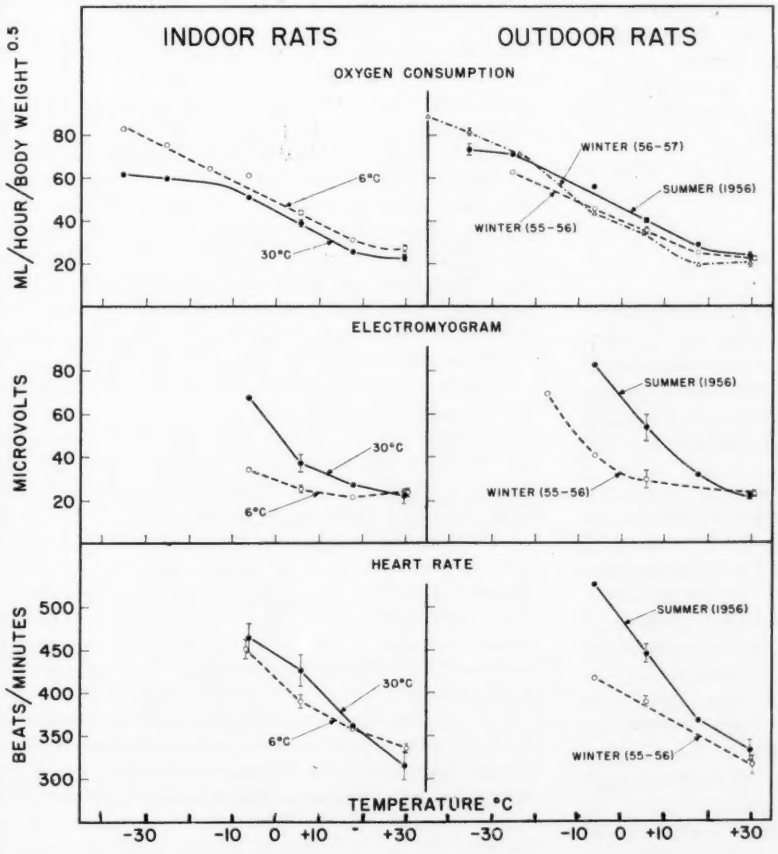


FIG. 5. O_2 consumption, electromyograms and heart rates of 30°C- and 6°C-acclimated rats and summer- and winter-acclimatized rats. From Heroux *et al.* (5).

metabolism, which is reached at about −15°C (fig. 3- for the 30°C acclimated rat, and at considerably lower temperatures for the cold-acclimated rat. Because heat production and body temperature are falling rapidly at temperatures below −10°C in warm-acclimated rats, the true peak rates can be seen only during the first 20 minutes of exposure (8). See also figure 1, deer mice. In tests lasting 20–50 minutes or 60–180 minutes, the average heat production has already fallen to quite low levels, depending on the temperature.

The elevation of heat production (fig. 3) and maintenance of warmer peripheral temperatures (table 2) with only slight elevation of central temperature signifies a decrease in body insulation in cold-acclimated rats. The acclimation-dependent changes in body insulation measured at the critical temperature have been summarized for a number of species in table 1 (4); there is a general decrease resulting from acclimation to cold, coincidental with an elevation of thermoneutral heat production.

The development of cold acclimation requires a period of time usually estimated to be from 2 to 6 weeks by various observers. During this time there is a gradual increase in cold resistance (1, 3), an increase in food consumption (10, 11), an elevation of basal metabolic rate (many authors), an elevation of peripheral (6, 7) and sometimes central (12) temperatures, a decrease in shivering and an increase in nonshivering heat production (13–15) and other associated physiological and biochemical changes.

SEASONAL ACCLIMATIZATION

Animals exposed to seasonal changes of environment in nature are subjected to a fluctuating instead of a constant or chronic thermal experience as well as to the influence of environmental factors other than temperature. It is therefore pertinent to enquire to what extent seasonal and temperature-induced adjustments resemble each other.

During the winter, the body insulation of furred animals is increased. This has been demonstrated for the larger mammals (arctic fox, porcupine) by Irving *et al.* (16) who found a lowering of the critical temperature during the winter. The enhanced insulation could provide for a lowering of temperature tolerance limits by approximately 35°C (9). A comparable lowering of the critical temperature in an aquatic mammal, the harbor seal, has been found by Hart and Irving (17). It has been previously pointed out (9) that this tendency for greater insulation during the colder period of the year is essentially opposite to that found during acclimation to cold.

In the larger land mammals a major part of the seasonal change in insulation (fig. 4) is presumably due to the change in fur insulation (18). Since the latter is much less in the smaller mammals, it is to be expected that metabolic compensation for cold temperatures should occur during the winter. In naturally occurring species, evidence of metabolic acclimatization has been reported only for house sparrows (19) and deer mice (20). In both species, the acclimatization was manifested by an increased ability to survive in the cold and an enhanced capability to produce heat.

TABLE 2. *Comparison of Insulative and Metabolic Properties of Indoor and Outdoor White Rats**

Measurements	Indoor Rats		Outdoor Rats	
	30°C	6°C	Summer	Winter
Survival time (min.)	123	575	178	437
O_2 consumption at 30°C ($ml/hr/gm^{0.5}$)	22.8	26.7	22.9	21.5
O_2 consumption at 6°C ($ml./hr/gm^{0.5}$)	38.2	43.4	39.5	34.5
Skin temperature at 6°C, back	33.4	34.4	34.1	31.2
Skin temperature at 6°C, tail	10.4	11.2	12.9	11.6
Pelage insulation ($°C/Cal/m^2/hr$)	0.31	0.31	0.27	0.36

* From Heroux *et al.* (5, 7).

A further study of seasonal changes was made by Heroux *et al.* (5, 7), who placed white rats, in groups of 10 with bedding, outside during the summer and winter at Ottawa. Data obtained on outdoor rats are compared with those of warm- and cold-acclimated indoor rats in figure 5. Changes in peak metabolic rates and shivering were similar in indoor and outdoor rats. In both groups, the cold-exposed rats developed an increased capability to produce heat and a greater nonshivering heat production as shown by the electrical activity of the muscles at different temperatures. The survival time at −35°C was increased to about the same extent in indoor and outdoor cold-exposed rats (table 2).

In other respects, however, the adjustments of indoor and outdoor rats were quite different. The outdoor winter rats had a lower thermoneutral metabolic rate (MR 30°) and lower rates at all temperatures above −10°C than the indoor cold-acclimated rats. The latter had a higher MR 30° and higher rates than warm-acclimated rats. The rates below peak levels, lower in winter than in summer rats, were due in part to greater pelage insulation (table 2), but also to lower peripheral temperatures. For acclimated rats, these trends were again reversed.

It is apparent that the differences in the thermal experience and the concomitant effects of other environmental factors have led to important differences in the metabolic and insulative patterns of the adaptive processes leading to the same enhancement of cold resistance. The resemblance of seasonal acclimatization in the white rat to that in certain native species will interest the comparative physiologist, whereas the differences in metabolic patterns between indoor and outdoor rats will be of interest to the physiologist and biochemist.

REFERENCES

1. BLAIR, J. R., J. M. DIMITROFF AND J. E. HINGELEY. *Fed. Proc.* 10: 15, 1951.
2. SELLERS, E. A., S. REICHMAN AND N. THOMAS. *Am. J. Physiol.* 167: 644, 1951.
3. HART, J. S. *Can. J. Zool.* 31: 80, 1953.
4. HART, J. S. *Can. J. Zool.* 31: 99, 1953.
5. HEROUX, O., F. DEPOCAS AND J. S. HART. *Can. J. Biochem. Physiol.* 37: 473, 1959.
6. CARLSON, L. D. In: *Cold Injury*. Trans. 3rd conf. New York: Macy, 1954.
7. HEROUX, O. *Can. J. Biochem. Physiol.* 37: 1247, 1959.
8. DEPOCAS, F., J. S. HART AND O. HEROUX. *J. Appl. Physiol.* 10: 393, 1957.
9. HART, J. S. *Rev. can. biol.* 16: 133, 1957.
10. SEALANDER, J. A. *J. Mammal.* 33: 206, 1952.
11. COTTLE, W. AND L. D. CARLSON. *Am. J. Physiol.* 178: 305, 1954.
12. GELINEO, S. *Ann. physiol. physiochim. biol.* 10: 1083, 1934.
13. SELLERS, E. A., J. W. SCOTT AND N. THOMAS. *Am. J. Physiol.* 177: 372, 1954.
14. HART, J. S., O. HEROUX AND F. DEPOCAS. *J. Appl. Physiol.* 9: 404, 1956.
15. COTTLE, W. H. AND L. D. CARLSON. *Proc. Soc. Exper. Biol. & Med.* 92: 845, 1956.
16. IRVING, L., H. KROG AND M. MONSON. *Physiol. Zool.* 28: 173, 1955.
17. HART, J. S. AND L. IRVING. *Can. J. Zool.* 37: 447, 1959.
18. HART, J. S. *Can. J. Zool.* 34: 53, 1956.
19. DAVIS, E. A. *Auk* 72: 385, 1955.
20. HART, J. S. AND O. HEROUX. *Can. J. Zool.* 31: 528, 1953.

Calorigenesis from various organ systems in the whole animal[1]

FLORENT DEPOCAS

Division of Applied Biology, National Research Council, Ottawa, Canada

DEPOCAS, FLORENT. *Calorigenesis from various organ systems in the whole animal*. Fed. Proc. 19, Supp. No. 5: 19–24. 1960.—The capability of cold-acclimated rats to produce heat by means other than shivering is now well demonstrated. There is, however, disagreement on the site of origin of this thermogenesis. Recent work on the ability of functionally eviscerated, cold-acclimated rats to increase their oxygen consumption on exposure to cold points to extra-abdominal tissues as possible sites for nonshivering thermogenesis. Data on the ability of functionally eviscerated, cold-acclimated rats, as well as sham-operated cold-acclimated rats, to respond to noradrenaline brings additional evidence for the importance of extrahepatic tissues as the site of nonshivering thermogenesis.

WHICH ARE THE ORGANS concerned with extra heat production of mammals exposed to cold? And how is the normal pattern of heat production in the cold altered by previous acclimation to a cold environment? These are the two problems to be examined in this presentation.

It is quite generally accepted that shivering is the most important means of heat production in the normal animal exposed to cold, and there is little evidence for extensive participation of tissues other than muscles in the cold-induced thermogenesis of normal animals (1). One of the best justifications for this statement has been given by Cottle and Carlson (2), who found very little increase in oxygen consumption in the fully curarized warm-acclimated rat exposed to cold.

For a number of mammalian species, however, quite an extensive literature exists on the presumed role of the abdominal organs in the metabolic response to cold as assessed by tissue or blood temperature measurements (1). Most of the data provided in these studies suffer from inadequate measurements of the variables required for a valid assessment of the proportion of the total extra heat production due to the liver or intestines or other organs of the animals exposed to cold. Satisfactory proof of the existence of nonshivering thermogenesis in an organ of a normal or warm-acclimated animal will require simultaneous measurements of arteriovenous differences in oxygen content and rate of flow of blood through the organ to be made before and after exposure to cold. Techniques for achieving this aim seem inadequate at the present time.

If the presence of nonshivering thermogenesis in the warm-acclimated animal is still doubtful, its occurrence in the cold-acclimated rat is well accepted. Sellers *et al.* (3) observed a decrease in the electrical activity of muscles of cold-acclimated rats exposed to cold as compared with room-temperature rats similarly treated. These observations were further extended by Heroux *et al.* (4), who made simultaneous measurements of total oxygen consumption and electrical activity of muscle in

[1] Contribution from the Division of Applied Biology, National Research Council, Canada; issued as N.R.C. No. 5962.

anesthetized warm- and cold-acclimated rats exposed to cold. The cold-acclimated rats gave a greater metabolic response with hardly any muscle action potentials being recorded. This study was further extended to show the progressive disappearance of shivering in unanesthetized rats during acclimation to a cold environment (5). Cottle and Carlson (2) then gave the definitive proof by showing that curarized cold-acclimated rats not only could increase their oxygen consumption but could maintain almost perfect thermal balance when the environmental temperature was slowly lowered from 30° to 6°C. We have repeated these experiments and obtained results in complete agreement with those of Cottle and Carlson (2).

Nonshivering thermogenesis exists in the white rat, but in which organ does it take place? Is there a substitution of the heat production of shivering by an increased heat production of the abdominal viscera? Or is it possible that the large muscle mass could produce heat without mechanical activity in the cold-acclimated rat by being responsive to hormonal stimulation? Or, possibly, all organs and tissues could be equally affected, each producing heat according to its mass.

When this problem was encountered, little work had been done with cold-acclimated animals in this respect. Much emphasis was then placed on the observations of You and Sellers (6) that liver slices from rats acclimated to cold showed a greater *in vitro* oxygen consumption and succinoxidase content than did liver slices from room-temperature acclimated rats. Weiss (7) later confirmed this increase in O_2 consumption of liver but demonstrated further that other tissues, the muscle in particular, also showed the same effect.

However, one can wonder about the significance of these results in relation to the well-proved ability of rats to transiently raise their heat production within a few minutes following exposure to cold (8), since the higher level of oxygen consumption of the cold-acclimated rat is apparent at all exposure temperatures. Nonshivering thermogenesis should not be a permanent manifestation of a tissue but be subject to being turned on and off, just like shivering in the warm-acclimated rat, in response to changes in the environmental temperature. It can be argued that the excess oxygen consumption of the liver slices of the cold-acclimated rat is small because the liver *in vitro* is not subjected to the controlling influences present *in vivo*, but the argument does not validate the interpretation of a direct contribution of liver to cold thermogenesis. It is fortunate in a way that muscle and abdominal viscera have been opposed as the source of nonshivering thermogenesis because it is rather easy to measure the O_2 consumption of an eviscerated rat in the warm and in the cold environment and thus to estimate the contribution of the abdominal viscera to cold thermogenesis. Admittedly, eviscerating a rat is a drastic operation. The liver is an important organ with numerous essential functions, but Ingle (9) has shown that eviscerated rats given glucose and insulin can live an average of 33 hours, and Russel (10) gives a survival time of approximately 2 hours for functionally eviscerated rats not given glucose. If experiments are restricted to the initial response to cold, enough time is available for adequate measurements of oxygen consumption. This idea has been followed in three sets of experiments (11).

In the first set, illustrated in figure 1, the oxygen consumption and muscle electrical activity of barbital-anesthetized warm- and cold-acclimated rats were measured before and after functional evisceration at 30° and 6°C. The functional evisceration technique consisted of ligating the inferior mesenteric artery, the coeliac and superior mesenteric arteries, and the portal vein and hepatic artery.

There was no significant difference between the increases in O_2 consumption by the eviscerated rats and the sham-operated, cold-acclimated rats exposed to cold

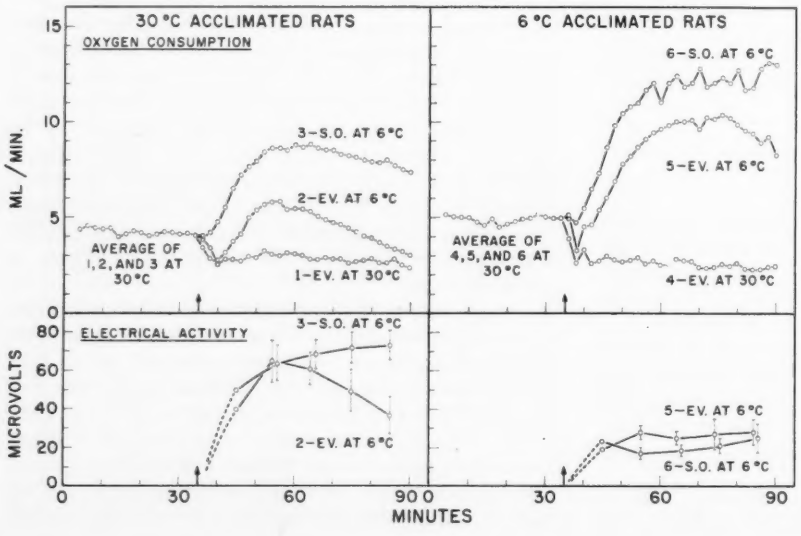


FIG. 1. Average O_2 consumption and muscle electrical activity of barbital-anesthetized 30°C and 6°C acclimated rats: at 30°C (average O_2 consumption of all similarly acclimated rats given for interval 0–35 min.); at 30°C after evisceration (*groups 1* and *4*); at 6°C after evisceration (*groups 2* and *5*); and at 6°C after sham-operation (*groups 3* and *6*). *Arrow* indicates time of evisceration or transfer to 6°C or both. All groups consisted of 5 animals except *group 3*, in which there were 6.

(7.33 ± 0.35 and 7.25 ± 0.66 ml O_2 per minute, respectively), and this without any appreciable difference in shivering between the two groups. Evisceration in the warm-acclimated rats affected both oxygen consumption and shivering, thereby pointing to the probable role of the liver in providing substrates required by the muscles. The lack of effect of evisceration on the cold-induced rise in O_2 consumption in the cold-acclimated rats is quite striking but as the animals still exhibited some shivering, further experiments were conducted in order to eliminate this variable.

The same procedures were then carried out in curarized cold-acclimated rats (fig. 2). In this case results were not as clear. Evisceration still produced a large drop in O_2 consumption and exposure of the sham-operated curarized rats to cold produced a large increase in O_2 consumption which was not completely suppressed by evisceration after the rise in O_2 consumption had taken place. Exposing the eviscerated, curarized, cold-acclimated rats of 6°C did not induce a significant rise in O_2 consumption.

Thus the picture for the curarized cold-acclimated rats was inconsistent. However, tubocurarine, besides

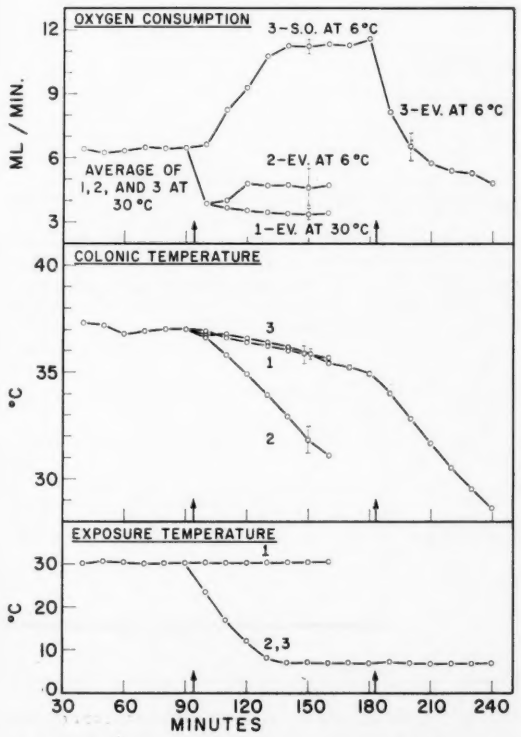


FIG. 2. Average O_2 consumption and rectal temperature of curarized 6°C acclimated rats: at 30°C (average values of all rats given for interval 40–90 min.); at 30°C after evisceration (*group 1*, 5 rats); at 6°C after evisceration (*group 2*, 8 rats); and at 6°C after sham-operation followed by evisceration (*group 3*, 5 rats). *First arrow* indicates time of evisceration of animals in *group 3*. Average exposure temperature for the different groups of rats is also given.

blocking the neuromuscular junction, also increases plasma glucose concentration to very high values. Disturbances in carbohydrate balance in the rat may be so profound as to make the secondary effects of evisceration more damaging to the curarized rat.

In a third set of experiments (fig. 3), the oxygen consumption of eviscerated or sham-operated warm- and cold-acclimated rats, curarized after the increase in O_2 consumption had taken place in the cold, was measured. This was done in order to estimate the contribution of shivering to the extra heat production. In this experiment fairly clear results were obtained. Curarization of the sham-operated and eviscerated warm-acclimated rats abruptly lowered the O_2 consumption to levels observed before exposure to cold. Curarization of the sham-operated cold-acclimated rats hardly altered the level attained, and in the eviscerated cold-acclimated rat O_2 consumption fell but stayed well above the initial level during the 45 minutes of observation.

Taken together these results are not consistent with the hypothesis of a major contribution of heat production by the abdominal viscera in either the warm- or cold-acclimated rat exposed to cold. This conclusion is, of course, limited to short periods following the beginning of cold exposure and is not meant to imply that the eviscerated cold-acclimated rat can withstand cold exposure as well as the normal rat.

In recent experiments designed to determine whether or not liver contributes to nonshivering thermogenesis, Kawahata and Carlson (12) failed to detect any changes in oxygen tension in liver and in liver blood flow, or any difference between liver and rectal temperature which could account for the increased oxygen consumption of curarized cold-acclimated rats exposed to cold. These results are essentially in accord with our conclusions and point to nonvisceral tissues as possible sites of nonshivering thermogenesis. It is yet impossible to implicate a specific tissue but it can be suspected that the large muscle mass of the eviscerated rat plays some role in the response.

The next question to answer is what are the substances which induce this increase in O_2 consumption. The work of Hsieh and Carlson (13) points strongly to noradrenaline as the mediator of nonshivering thermogenesis, since cold-acclimated rats show a larger increase in O_2 consumption after noradrenaline injection than do warm-acclimated rats on administration of this drug. Hyperglycemia is not usually observed in cold-exposed animals and always results from injection of adrenaline.

The work of Hsieh and Carlson was recently confirmed and extended (14). Instead of giving a single dose of noradrenaline, the amine was infused intravenously at a known constant rate and the O_2 consumption measured continuously in the tracheotomized anesthetized animal.

Figure 4 illustrates a typical result obtained with noradrenaline in a cold-acclimated rat. Noradrenaline was infused into the femoral vein 20 minutes after start of oxygen consumption measurements. During the in-

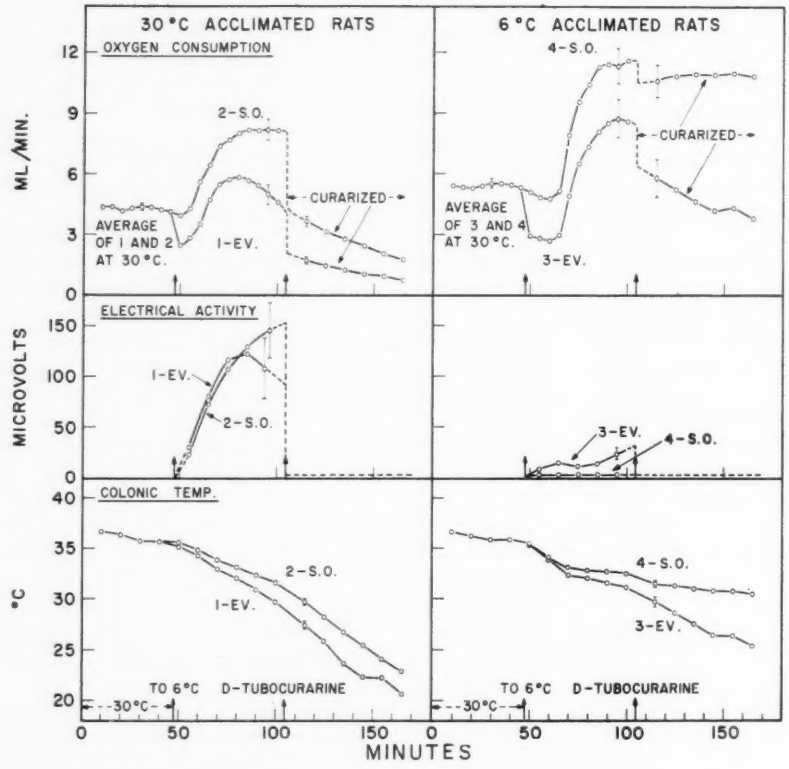


FIG. 3. Average O_2 consumption, muscle electrical activity and rectal temperature of barbital-anesthetized 30°C and 6°C acclimated rats: at 30°C (average values of all similarly acclimated rats given for interval 10–45 min.); at 6°C after evisceration (*groups 1* and *3*); and at 6°C after sham-operation (*groups 2* and *4*). *First arrow* indicates time of evisceration or transfer to the cold room or both. *Second arrow* indicates time of curarization of all animals. There were 3 rats per group except *group 3*, in which there were 5.

fusion, oxygen consumption increased for 20 to 30 minutes and then became more or less stable. This particular animal was receiving 1.4 μg noradrenaline free base (NA) per minute and the O_2 consumption reached a value three times basal. The area delimited by the curve of oxygen consumption vs time during NA infusion minus the area corresponding to the initial O_2 consumption was termed the metabolic response.

In the first experiment the metabolic response of warm- and cold-acclimated rats to various doses of intravenously infused noradrenaline was measured (fig. 5). Four warm-acclimated rats showed no response at all to noradrenaline infusion. Although quite variable, the results with cold-acclimated rats indicated a definite relationship between the metabolic response and the logarithm of the dose of noradrenaline infused per minute. Using a dose of NA of 1 μg/min., which gave a large difference between warm- and cold-acclimated rats, the metabolic response of rats undergoing acclimation to cold compared with rats maintained in a warm room was then tested (fig. 6). All these rats had spent 14–18 days in a room at 30°C before the experiment began. Warm-acclimated rats gave a small response which tended to decrease with time spent in the warm room. In the rats exposed to cold the metabolic response to continuous infusion of 1 μg NA increased with time spent in the cold up to a maximum value which was attained after about 30 days exposure.

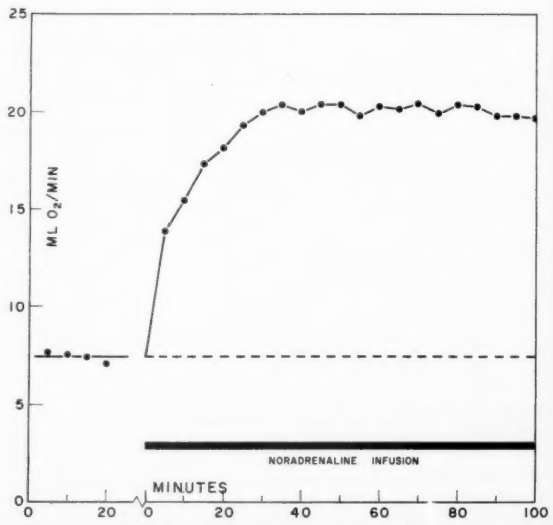


FIG. 4. Typical increase in O_2 consumption observed during infusion of noradrenaline into an anesthetized cold-acclimated rat at 20°C. The 369-gm animal had been at 6°C for 61 days and was given 1.48 μg noradrenaline base per min. i.v. from 0 to 100 min. The area between the O_2 consumption curve and the hatched curve (corresponding to average initial O_2 consumption) was taken as the metabolic response.

Summarizing the evidence in favor of NA being the mediator of nonshivering thermogenesis in the cold-acclimated rat, there is:

1) Greater sensitivity of the cold-acclimated rat to NA injected intramuscularly or intravenously (13, 14).

2) No intense hyperglycemia associated with the increased metabolism as would be obtained with similar doses of adrenaline, and also no hyperlactacidemia (13).

3) The observation that noradrenaline is more effective than adrenaline in preventing the fall in O_2 consumption caused by hexamethonium in curarized cold-acclimated rats exposed to cold (15).

4) The magnitude of the metabolic response to NA infusion which can approach values of O_2 consumption observed in rats exposed to environments at $-25°C$ (13).

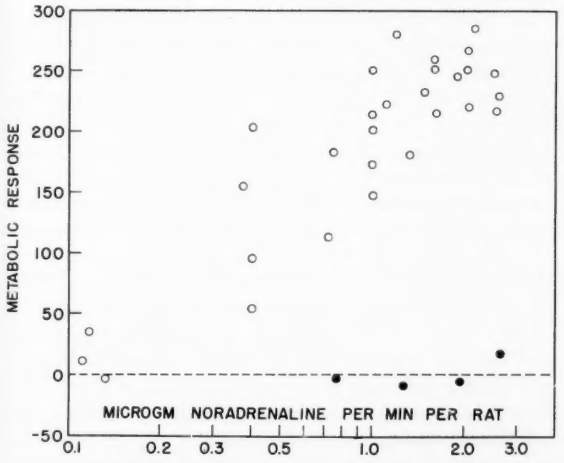


FIG. 5. Metabolic response to i.v. infused L-noradrenaline bitartrate in 30°C acclimated (*solid circles*) and in 6°C acclimated (*open circles*) rats. Metabolic response is in cm² and corresponds to the area under the curve of O_2 consumption vs. time during noradrenaline infusion minus the area corresponding to the initial O_2 consumption in the same period.

5) The striking inverse relation between the increase in metabolic response to NA infusion during acclimation to cold and the simultaneous decrease in muscle electrical activity (about 4 weeks). This can be interpreted as a substitution of nonshivering thermogenesis under the control of noradrenaline for heat production by shivering (14, 15).

After this preliminary establishment of the noradrenaline effect in the cold-acclimated rat, the main topic of this paper can be considered again. If nonshivering thermogenesis in the cold-acclimated rat is independent of the abdominal viscera and if noradrenaline is the mediator of this response, noradrenaline should be as effective in raising the oxygen consumption of the eviscerated cold-acclimated rat as it would be in the sham-operated one. The answer is given in figure 7 (14).

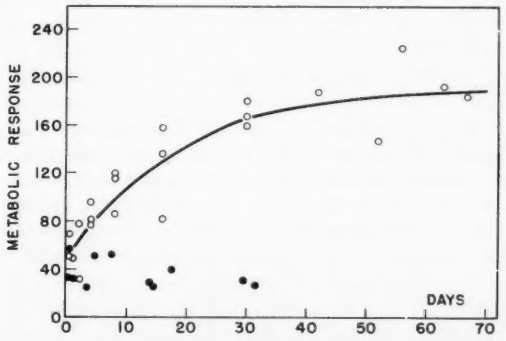


FIG. 6. Metabolic response to i.v. infused L-noradrenaline bitartrate at a level of 1 μg free base/min./rat in rats previously maintained at 30°C (*solid circles*) and 6°C (*open circles*). Metabolic response is in cm² and corresponds to the area under the curve of O_2 consumption vs. time during noradrenaline infusion minus the area corresponding to the initial O_2 consumption in the same period. All rats had spent 14–18 days at 30°C before time 0. Curve calculated from the equation $Y = 193 - 145$ exp. $- 0.0051\ X$, where Y is metabolic response and X is time in days.

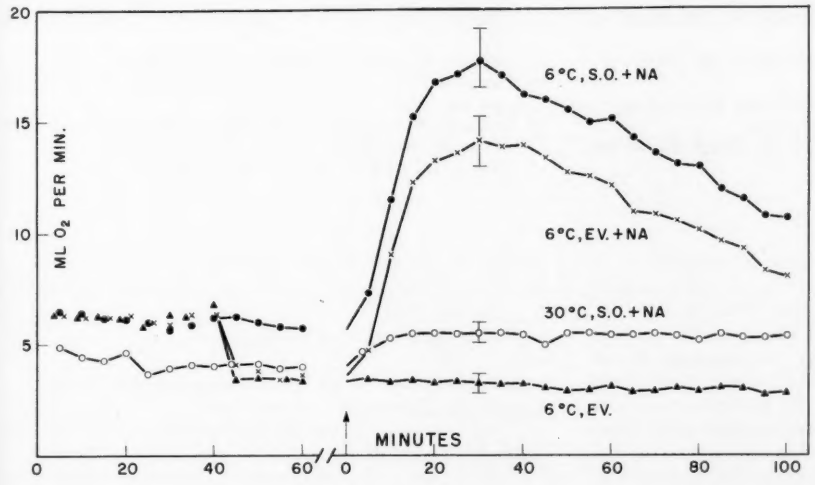


FIG. 7. Average O_2 consumption of barbital-anesthetized cold-acclimated rats (3 per group): functionally eviscerated and infused with 0.1% sodium bisulfite in saline (6°C, EV.); functionally eviscerated and infused with noradrenaline (in 0.1% sodium bisulfite in saline) at a dose of 1 μg/min. (6°C, EV. + NA); sham-operated and infused with noradrenaline at the same dose level (6°C, S.O. + NA). Average O_2 consumption of 2 warm-acclimated rats, sham-operated and infused with noradrenaline (30°C, S.O. + NA), is also given. *Arrow* indicates start of infusion which lasted 100 min. *Vertical bars* indicate total range of variation.

Evisceration produced a 40 % drop in O_2 consumption. Infusing noradrenaline into the sham-operated 6°C rats induced a maximal average increase of 11.6 ml O_2 (range 10.8–12.5) while infusing the eviscerated 6°C rats induced a maximal average of 10.3 ml (range 8.7–11.4), the difference being insignificant. This graph is very similar to the one showing the metabolic response of functionally eviscerated or sham-operated cold-acclimated rats to cold exposure. The results are again in accord with the concept that the abdominal viscera are not the site of nonshivering thermogenesis and add one more piece of evidence in favor of noradrenaline as the mediator of nonshivering thermogenesis.

Very convincing evidence that the liver and other abdominal organs are not directly involved in the production of heat by means other than shivering in the cold-acclimated rat has thus been acquired. This is negative evidence which should at least be of help in the planning of future work. There is still no direct evidence which would permit identification of the tissue involved, but the muscles should be considered as a possible site for nonshivering thermogenesis in the cold-acclimated rat.

That the potential for very large increases in oxygen consumption already exists in this tissue is manifested in the running and shivering of the warm-acclimated rat when in the cold. In shivering, muscle fibers are stimulated through release of acetylcholine at the motor end plate. The net result is a release of energy stored in ATP and phosphocreatine with stimulation of the mechanisms for restoration of the initial levels of these substances with concomitant increase in oxygen consumption. During acclimation to cold, heat production due to shivering slowly disappears and presumably is replaced by heat production induced by noradrenaline in the same tissue. Possibly the same over-all chemical reactions may be involved but control would have shifted from parasympathetic to sympathetic elements. This hypothesis finds its parallel in the dinitrophenol induced increase of oxygen consumption in muscle (16).

Before we can accept any such theory much work remains to be done. It must be demonstrated by direct methods that muscle tissue of a cold-acclimated animal can increase its oxygen consumption without electrical activity when the animal is exposed to cold or administered noradrenaline at the proper dosage. Experimentally, this could be achieved by measuring A-V differences in oxygen content and amount of blood flowing through a well-defined muscle mass in a curarized cold-acclimated animal.

If muscle participation in nonshivering thermogenesis is demonstrated, one is then faced with the problem of explaining sympathetic involvement in the effect. As demonstrated by Cottle and Carlson (2), adrenal demedullation lowers the cold response of the curarized cold-acclimated rat and Hsieh *et al.* (15) have demonstrated that ganglionic blocking and sympatholytic substances prevent this response. Direct sympathetic innervation of striated muscle is a highly debated question (17), discussion of which will be left to more competent investigators in the field of neurophysiology.

The biochemical implications of these findings, so closely allied to the problems of the nature of muscle contraction and control of cellular metabolism, are sufficiently fascinating to provide great incentive for future work on this presently puzzling phenomenon of nonshivering thermogenesis.

REFERENCES

1. Chatonnet, J. *J. Physiol. (Paris)* 51: 319, 1959.
2. Cottle, W. and L. D. Carlson. *Proc. Soc. Exper. Biol. & Med.* 92: 845, 1956.
3. Sellers, E. A., J. W. Scott and N. Thomas. *Am. J. Physiol.* 177: 372, 1954.
4. Heroux, O., J. S. Hart and F. Depocas. *J. Appl. Physiol.* 9: 399, 1956.
5. Hart, J. S., O. Heroux and F. Depocas. *J. Appl. Physiol.* 9: 404, 1956.
6. You, R. W. and E. A. Sellers. *Endocrinology* 49: 374, 1951.
7. Weiss, A. K. *Am. J. Physiol.* 177: 201, 1954.
8. Depocas, F., J. S. Hart and O. Heroux. *J. Appl. Physiol.* 10: 393, 1957.
9. Ingle, D. J. *Proc. Soc. Exper. Biol. & Med.* 69: 441, 1948.
10. Russel, J. A. *Am. J. Physiol.* 136: 95, 1942.
11. Depocas, F. *Canad. J. Biochem. & Physiol.* 36: 691, 1958.
12. Kawahata, A. and L. D. Carlson. *Proc. Soc. Exper. Biol. & Med.* 101: 303, 1959.
13. Hsieh, A. C. L. and L. D. Carlson. *Am. J. Physiol.* 190: 243, 1957.
14. Depocas, F. *Canad. J. Biochem. & Physiol.* 38: 107, 1960.
15. Hsieh, A. C. L., L. D. Carlson and G. Gray. *Am. J. Physiol.* 190: 247, 1957.
16. Issekutz, B., G. Hetenyi, M. Winter, M. Mozonyi and M. Forbath. *Acta Physiol.* 10: 327, 1956.
17. Hinsey, J. C. *Physiol. Rev.* 14: 514, 1934.

Discussion

L. D. CARLSON, R. E. BEYER, F. DEPOCAS, E. J. MASORO, H. T. HAMMEL

DR. CARLSON: One of the things that is most interesting to me is the fact that these discussions are in a field in which there are many competent people working, and I think Dr. Depocas has demonstrated this. Dr. Depocas has indicated that the answer to some of these questions is at the cellular level and actually much work is going on in this aspect right now. I would like to say also that there has been an intriguing paper by Donhoffer *et al.* (*Pflugers Arch.* 265: 104, 1957), showing that in the intermediate range (i.e. 20°C) rats cool, and as they cool their metabolism fluctuates in cycles over a period of minutes, increasing and decreasing. This fluctuation is matched by a change in the fluctuation of the temperature of the internal organs, but the muscle temperature continues to fall. I think this is one of the critical problems now facing us with respect to the questions Dr. Depocas presented. Muscle temperature continues to fall in these animals. Thus, in the investigation one is dealing with metabolism at temperatures below normal in the major mass of muscle.

DR. BEYER: Dr. Depocas, I noted that you used a barbiturate as anesthetic in your experiments. Certain barbiturates have been shown to have a profound *in vitro* metabolic effect (L. Ernster *et al. Exper. Cell Research* Supp. 3: 124, 1955). I wonder if you have attempted your experiments on lightly and deeply anesthetized animals in order to determine whether or not there is an effect of the anesthesia.

DR. DEPOCAS: All experiments I have reported involved animals anesthetized with sodium barbital at a dose of 290 mg/kg given intraperitoneally. The nonanesthetized cold-acclimated rat responds to noradrenaline infusion similarly to barbital-anesthetized rats (unpublished experiments). It may also be pointed out that Hsieh and Carlson discovered the strong calorigenic action of noradrenaline using cold-acclimated rats which were not anesthetized and my results are in qualitative agreement with theirs in regard to this effect.

DR. MASORO: I wonder if there might not be another explanation for the calorigenic action of norepinephrine in the cold-acclimated rat. Dr. Mike Schotz presented evidence at the Federation meetings this April that norepinephrine administration increases the levels of plasma nonesterified fatty acids (NEFA) even more than does epinephrine. Dr. Ed Neptune in several published reports has shown that fat can be the major metabolic fuel of skeletal muscle. Therefore, I wonder if norepinephrine acts calorigenically merely by making more fatty acid available to the skeletal muscle. Cold-acclimation then enables the skeletal muscle to oxidize the extra fatty acid substrate so made available. If such be the case one can see that norepinephrine could only cause an increased calorigenesis in the cold-acclimated animal.

DR. DEPOCAS: One is then left with having to explain how cold acclimation increases the capacity of muscles to oxidize the extra nonesterified fatty acids provided through noradrenaline action. However, noradrenaline could be a more potent mobilizer of NEFA in the cold-acclimated rat, and the calorigenic effect simply a resultant of substrate availability at the cellular level. Also, the noradrenaline effect must involve an increase in glucose oxidation since we have found no change in the proportion of respiratory CO_2 derived from glucose oxidation in cold-acclimated rats placed in environments at 30° or 6°C.

DR. HAMMEL: I wish to point out that the Australian aborigines do not produce extra heat during a cold night by either shivering or nonshivering thermogenesis.

Nonshivering thermogenesis and its endocrine control[1]

L. D. CARLSON

Department of Physiology and Biophysics, University of Washington School of Medicine, Seattle, Washington[2]

CARLSON, L. D. *Nonshivering thermogenesis and its endocrine control*. Fed. Proc. 19, Suppl. No. 5: 25–30. 1960.—Nonshivering thermogenesis designates an increase in heat production by an animal exposed to cold without detectable muscle activity as determined by the electromyogram. It may exist in varying degrees in the rat, rabbit, dog and man, but only in the rat has the effect of cold acclimation in enhancing this avenue of heat production been clearly shown. The enhanced heat production on cold exposure in a curarized animal is brought about by the autonomic nervous system and is suppressed by autonomic blocking agents and by sympatholytic drugs. Thyroidectomy reduces the response and confirms the role of thyroxin in the cold-acclimated animal. The calorigenic activity of epinephrine is potentiated and noradrenaline becomes markedly calorigenic.

[1] This research was supported by the U. S. Air Force under contract #AF41(657)-216 between the University of Washington and the Arctic Aeromedical Laboratory.

[2] Present address: Dept. of Physiology, College of Medicine, University of Kentucky, Lexington, Ky.

THE EVIDENCE FOR NONSHIVERING THERMOGENESIS comes in part from Keller's observations on gross shivering (1). He emphasized that cold-stimulated nonshivering heat production in dogs is just as distinct an entity as shivering heat production. Each has a separate and distinct group of nerve cells and a unique descending fiver tract in the hypothalamic gray matter and brain stem. Each is equally dependent upon impulses from its own efferent neurons. Electromyographic evidence also establishes the existence of nonshivering thermogenesis. Sellers *et al.* (2) and Hart *et al.* (3) described the decrease in shivering as exposure to cold continued. Carlson (4) observed a diminution in electrical activity from muscles of rabbits continuously exposed to cold and also saw a change in the nature of the electromyogram. Cottle and Carlson (5) described the marked changes in nonshivering thermogenesis which occur in the rat with continued exposure to cold. These results have been confirmed and extended by Depocas (6).

DuBois *et al.* (7) found a true chemical regulation[3] in some women studied and stated that the lack of significant change in the metabolism of men and some women with a change in the environment shows that there must be a chemical regulation which increases metabolism in the core of the body to compensate for the lowering of metabolism in the periphery.

[3] Because of confusion in the use of this term since Rubner defined it, 'nonshivering thermogenesis' is a better term.

Thus nonshivering thermogenesis appears to exist in varying degrees in the rat, rabbit, dog and man, but only in the rat has the effect of cold acclimation in enhancing this avenue of heat production been clearly shown. This change requires days or weeks and is definitely present in the rat after 3 weeks' exposure to 5°C. The following is a discussion of the role of the adrenal and thyroid glands in this response.

Cottle and Carlson's results (5) indicated partial involvement of the adrenal medulla in the nonshivering response (fig. 1). The oxygen consumption of curarized rats on a resuscitator was determined for 90 minutes at 30°C; the room was then cooled over a period of 40 minutes to 5°C and remained at this temperature. The intact cold-adapted rat maintained its rectal temperature with a marked rise in oxygen consumption. The response in similarly treated rats with their adrenals demedullated was smaller but still much greater than that of the nonacclimated controls. Note that the nonacclimated animals appeared to respond to cooling with an increased metabolism, but that the heat production was not sufficient to maintain body temperature, and the metabolism fell.

In attempting to elucidate the mechanism of this response, Hsieh and his co-workers (8) established that the sympathetic nervous system is involved in the response and that norepinephrine becomes definitely calorigenic. When the autonomic blocking agent hexa-

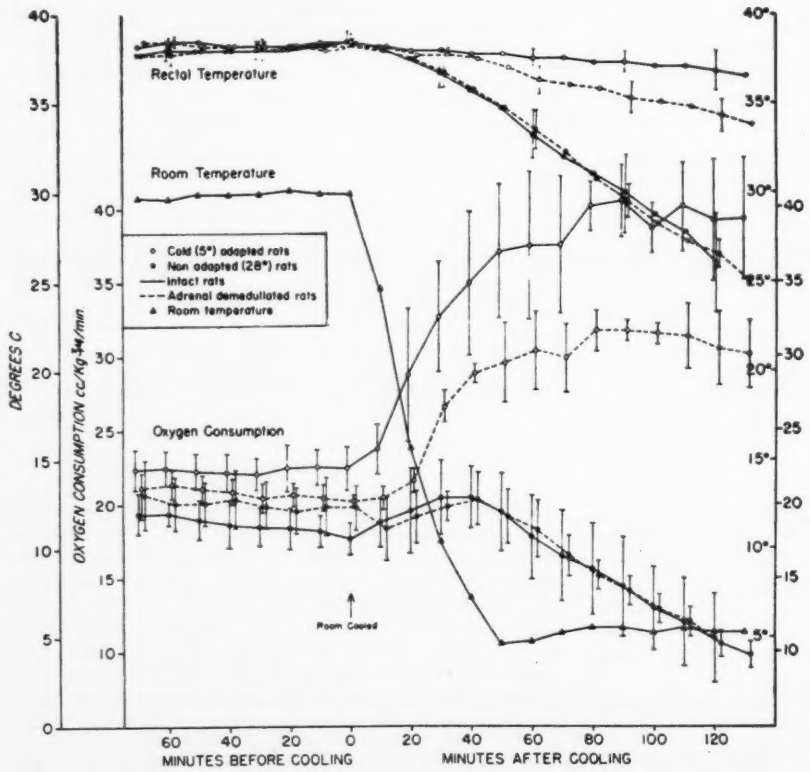


FIG. 1. Metabolic response of curarized rats to lowered ambient temperature. Mean O_2 consumption and rectal temperature of each group along with ambient temperature is plotted on *ordinate*. Standard deviations indicated by *vertical lines*. From Cottle and Carlson (9).

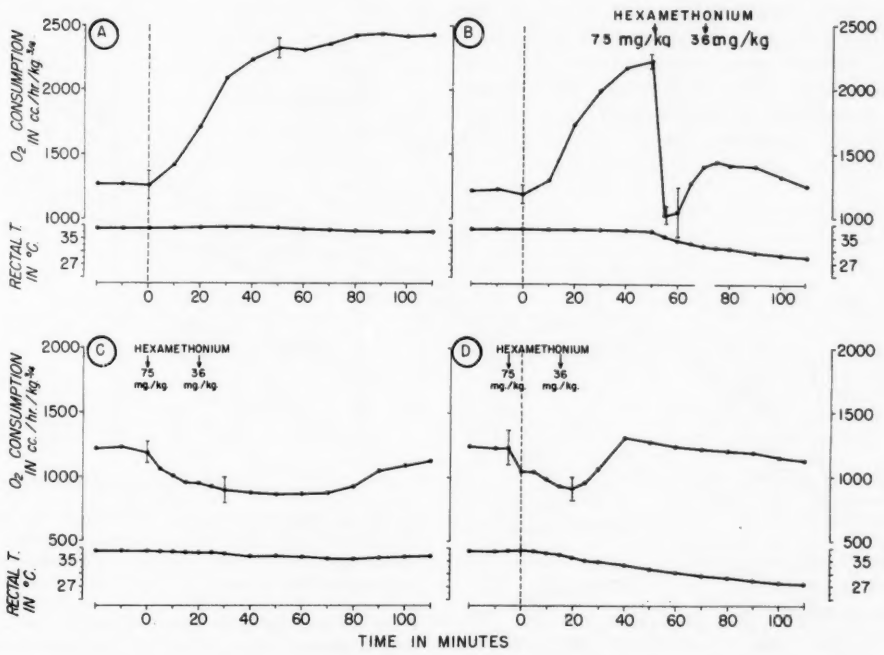


FIG. 2. O_2 consumption and rectal temperatures of curarized, cold-adapted rats receiving hexamethonium. Room temperature was lowered from 30°C to 5°C ± 1° in *A*, *B* and *D* at zero time; in *C* temperature was maintained at 30°C ± 1°. Hexamethonium was injected i.b. at points indicated by *arrows*. *Vertical bars* indicate standard deviation. Dots for rectal temperature cover range for standard deviation. Each point is the mean of 5 experiments. From Hsieh *et al.* (8).

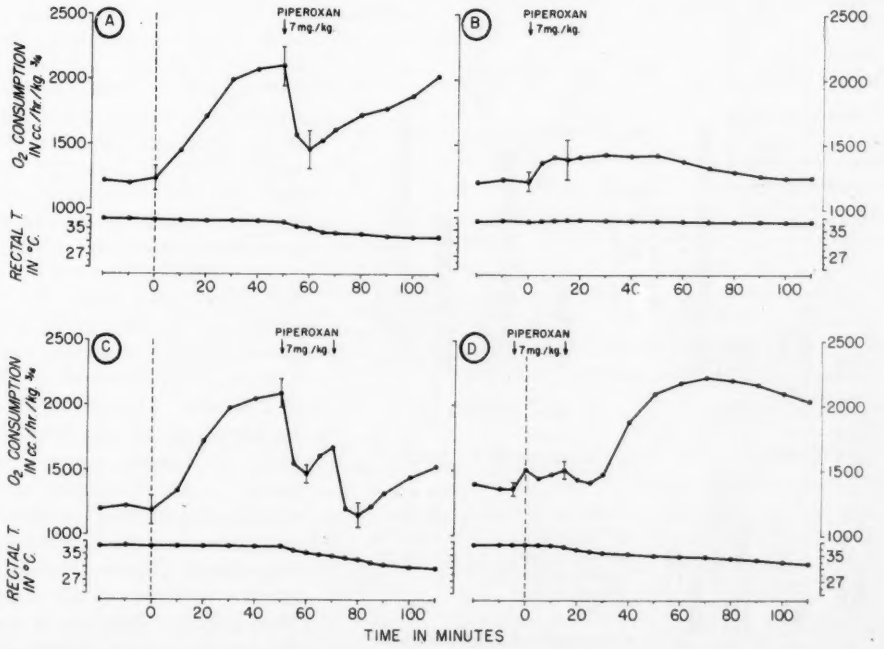


FIG. 3. O_2 consumption and rectal temperatures of curarized rats receiving piperoxan. Room temperature was lowered from 30°C to 5°C ± 1° in *A*, *C* and *D* at zero times; in *B* it was maintained at 30°C ± 1°. Piperoxan was injected i.b. at points indicated by *arrows*. *Vertical bars* indicate standard deviation of O_2 consumption. From Hsieh *et al.* (8).

methonium is administered before cold exposure, the thermogenic response to cold in the curarized acclimated rat is blocked; if hexamethonium is administered during exposure (fig. 2), the response is reduced. The adrenolytic drug piperoxan has the same effects (fig. 3). Norepinephrine, when administered to the cold-acclimated animal, is calorigenic whether the animal is at 30° or 5°C. Figure 4 shows the response at 30°C and indicates the marked rise in rectal temperature which accompanies this response. This discovery concerning norepinephrine indicates that its calorigenic role depends on the history of cold exposure of the animal and suggests that the norepinephrine from sympathetic endings is the natural mediator of the calorigenic response. Such mediation would allow the metabolic response to occur with the same time pattern as does shivering. The injection of epinephrine in the cold-acclimated rat causes a rise in blood glucose while injections of norepinephrine do not. Blood sugar does not increase significantly during cold exposure under the test conditions used by these workers (7).

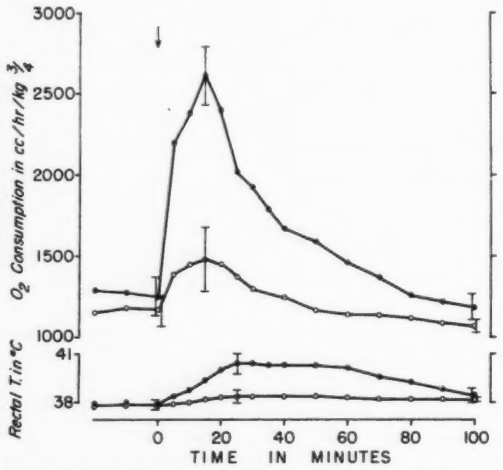


FIG. 4. Effects of L-noradrenaline, 0.2 mg/kg, on O_2 consumption and rectal temperature of cold-adapted rats (*solid circles*) and warm-adapted rats (*open circles*). Experiments were conducted at 30°C ± 1°. L-noradrenaline was injected intramuscularly at point indicated by *arrow*. *Vertical bars* indicate standard deviation. Each point represents the mean of 4 experiments. From Hsieh and Carlson (15).

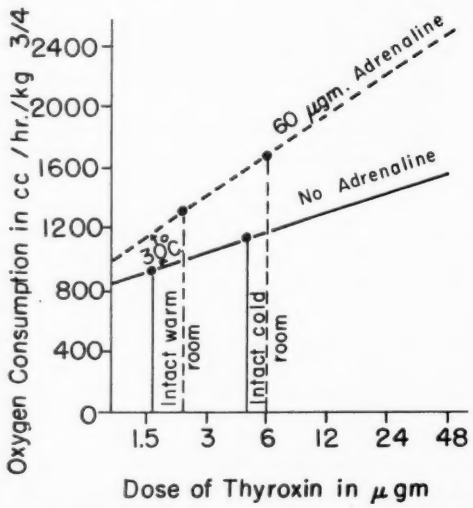


FIG. 6. Regression of O_2 consumption by thyroidectomized rats treated with daily doses of thyroxine plotted against the dose of thyroxin on a logarithmic scale. Thyroidectomized animals were considered to secrete 1 µg of thyroxine per day. *Solid line* represents O_2 consumption at 30°C without adrenaline. *Dotted line* represents O_2 consumption at 30°C 1 hour after 60 µg of adrenaline per 100 gm. b. w. i.m. *Dots* represent O_2 consumption at 30°C of intact controls and intact cold-acclimated rats, with and without adrenaline, interpolated on the thyroxine dose response curve. Modified from Swanson (13).

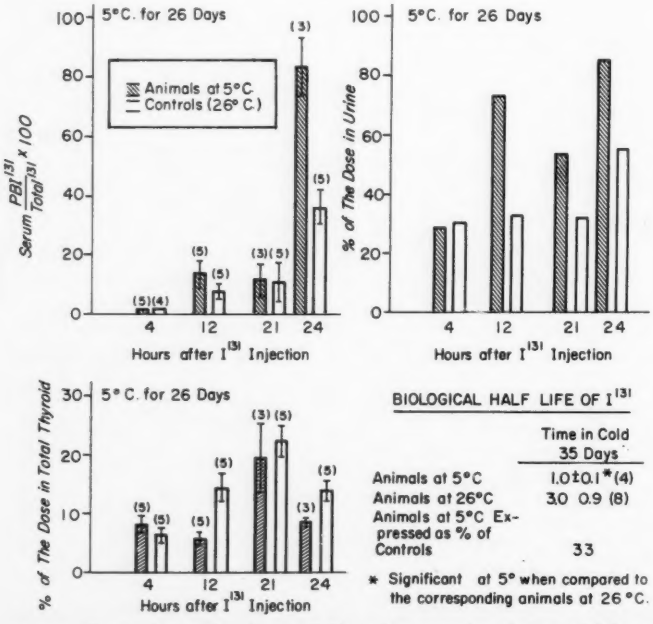

5°C. for 26 Days
Animals at 5°C.
Controls (26° C.)
Serum $\frac{PBI^{131}}{Total^{131}} \times 100$
% of The Dose in Urine
Hours after I^{131} Injection
5° C. for 26 Days
% of The Dose in Total Thyroid
BIOLOGICAL HALF LIFE OF I^{131}
Time in Cold 35 Days
Animals at 5°C 1.0±0.1*(4)
Animals at 26°C 3.0 0.9 (8)
Animals at 5°C Expressed as % of Controls 33
* Significant at 5° when compared to the corresponding animals at 26 °C.

FIG. 5. Conversion ratios (upper left), urine excretion (upper right) and thyroid content of I^{131} at 26 days. Biological half life is shown at the lower right. Modified from Cottle and Carlson (9).

It has been shown that cold acclimation is associated with an increase in thyroxin turnover and thyroxin requirement. The increase in thyroxin turnover has been illustrated by the I^{131} technique by Cottle and Carlson (9). Figure 5 is taken from this work and illustrates the various factors involved after about 4 weeks of exposure. The increased requirement for thyroxin has been illustrated by substitution techniques (10). Rats in the cold can survive, however, with lesser amounts of thyroxin (11). When man is exposed, nude, to 60°F for two weeks, his thyroxin utilization increases (12).

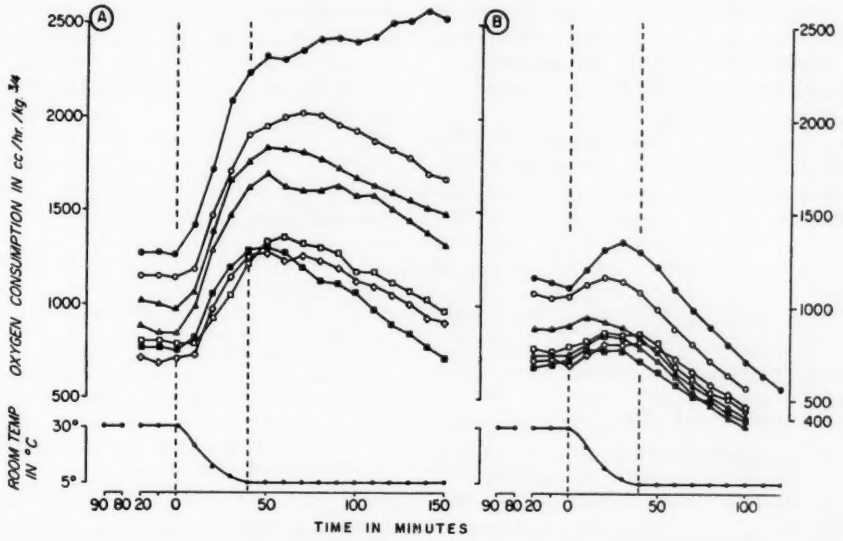


FIG. 7. O_2 consumption of curarized rats with room temperature at 30°C, during cooling to 5°C and while at 5°C. *A*: cold-adapted rats. *B*: warm-adapted rats. Each point represents the mean of 3–5 experiments. In *A*, *solid circle* = intact controls; *open circle* = 2 days postthyroidectomy; *solid triangle* = 4 days postthyroidectomy; *open triangle* = 6 days postthyroidectomy; *solid square* = 8 days postthyroidectomy; *open square* = 10 days postthyroidectomy; *open diamond* = 12 days postthyroidectomy. In *B*, *solid circle* = intact controls; *open circle* = 4 days postthyroidectomy; *solid triangle* = 8 days postthyroidectomy; *open triangle* = 12 days postthyroidectomy; *solid square* = 16 days postthyroidectomy; *open square* = 20 days postthyroidectomy; *open diamond* = 24 days postthyroidectomy. From Hsieh and Carlson (15).

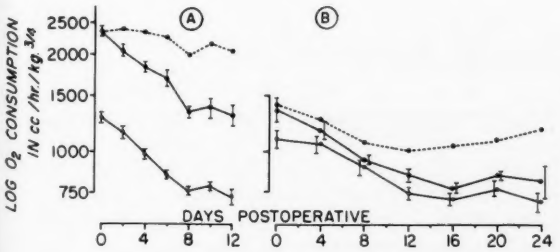


FIG. 8. O_2 consumption of curarized rats measured at 30°C and maximum response attained during cooling, plotted on a logarithmic scale against days after thyroidectomy. *A*: cold-adapted rats. *B*: warm-adapted rats. *Open circles* represent O_2 consumption measured at 30°C. *Dots* are maximal O_2 consumption attained during cooling. *Dotted line* represents maximal O_2 consumption corrected to body temperatures of 37.5°C. *Vertical lines* indicate S. E. From Hsieh and Carlson (15).

The calorigenic action of epinephrine is synergistic with thyroxin; this relationship has been investigated by Swanson (13). When thyroidectomized animals were given daily thyroxin, their metabolic rates increased with increasing dose. Under these conditions the effect of 60 μg of epinephrine was also dose-dependent (fig. 6). When nonthyroidectomized animals of control or acclimated groups were tested with 60 μg of epinephrine in oil intramuscularly, the response was greater in the acclimated group, and the relation of these points to the curves of graded dose of thyroxin was consistent with the increased turnover of thyroxin (fig. 6). Blood PBI does not appear to be increased in cold-acclimated rats (14).

Further elucidation of the role of thyroxin is derived from the work of Hsieh and Carlson (15), who found that the cold-induced nonshivering thermogenesis progressively decreased with time following thyroidectomy (fig. 7). When plotted semilogarithmically, both the metabolism at 30°C and maximum response at 5°C declined linearly with time (fig. 8). The half time for the fall of metabolism of the acclimated rat at 30°C was 3½ days as compared to 7 days in the nonacclimated group. There was little or no calorigenic response to epinephrine in the athyroid animal (13), yet the cold-acclimated athyroid animal still responded to cold exposure with an increased metabolism. Attempts at artificial acclimatization with thyroxin have not been successful (16). Some thyroid hormone is essential and without it the animal cannot achieve the metabolic rates necessary to maintain thermal equilibrium.

By tests, such as ability to survive at very low temperature, adrenal cortical hormones do not appear to be essential to the maintenance of cold acclimation (17), although they do appear to be required in greater than normal amounts on initial exposure to cold (18). Once cold acclimation is established it can be main ained by a constant and relatively low rate of administration of adrenal cortical hormones. The actual production or turnover of these hormones in the cold-acclimated animal is not known.

It must be emphasized that the results described above

were obtained in animals chronically exposed to cold. Intermittent exposure leads to an increased tolerance to cold, but may involve other patterns of endocrine response (19). Furthermore, the role of insulin and glucagon are yet to be investigated.

In summary, nonshivering thermogenesis exists in animals in varying degrees, and is controlled via the sympathetic nervous system. The most marked example studied is in the white rat continuously exposed to cold. Although the metabolic capability of the animal appears to be increased by various hormones, no single hormone represents the cause for the acclimation. Rather they provide some of the necessary mechanisms involved in the response.

During the course of my work in this field, I have enjoyed the collaboration of Drs. Arnold Hsieh, Walter and Merva Cottle, and Heidi Swanson.

REFERENCES

1. KELLER, A. D. In: *The Physiology of Induced Hypothermia*, edited by R. D. DUPPS. *Nat. Acad. Sc.-Nat. Res. Council Publ.* 451, 1956.
2. SELLERS, E. A., J. W. SCOTT AND N. THOMAS. *Am. J. Physiol.* 177: 372, 1954.
3. HART, J. S., O. Heroux and F. Depocas. *J. Appl. Physiol.* 9: 404, 1956.
4. CARLSON, L. D. In: *Cold Injury—Third Conference*, edited by M. I. Ferrer. New York: Macy, 1954.
5. COTTLE, W. H. AND L. D. CARLSON. *Proc. Soc. Exper. Biol. & Med.* 92: 845, 1956.
6. DEPOCAS, F.. *Canad. J. Biochem. & Physiol.* 361: 691, 1958.
7. DUBOIS, E. F., F. G. EDBOUGH, JR. AND J. D. HARDY. *J. Nutrition* 48: 257, 1952.
8. HSIEH, A. C. L., L. D. CARLSON AND G. GRAY. *Am. J. Physiol.* 190: 247, 1957.
9. COTTLE, MERVA AND L. D. CARLSON. *Endocrinology* 59: 1, 1956.
10. WOODS, R. AND L. D. CARLSON. *Endocrinology* 59: 323, 1956.
11. SELLERS, E. A. AND S. S. YOU. *Am. J. Physiol.* 163: 81, 1950.
12. INGBAR, S. H. AND D. E. BASS. Unpublished observations reported in *Cold Injury, Sixth Conference*, edited by S. M. Howath. New York: Macy, 1960.
13. SWANSON, HEIDI E.. *Endocrinology* 60: 205, 1957.
14. BONDY, P. K. AND M. A. HAGEWOOD. *Proc. Soc. Exper. Biol. & Med.* 81: 328, 1953.
15. HSIEH, A. C. L. AND L. D. CARLSON. *Am. J. Physiol.* 188: 40, 1957.
16. SELLERS, E. A., S. RUCHMAN AND N. THOMAS. *Am. J. Physiol.* 167: 644, 1951.
17. HEROUX, O.. *Am. J. Physiol.* 181: 75, 1955.
18. HEROUX, O. AND J. S. HART. *Am. J. Physiol.* 178: 449, 1954.
19. HEROUX, O., E. SCHONBAUM AND A. DES MARAIS. *Fed. Proc.* 18: 67, 1959.

Peripheral and central control of cold-stimulated thermogenesis[1]

ALLEN D. KELLER
Physiology Division, U.S. Army Medical Research Laboratory, Fort Knox, Kentucky

KELLER, ALLEN D. *Peripheral and central control of cold-stimulated thermogenesis.* Fed. Proc. 19, Suppl. No. 5: 30–32. 1960.—The homeotherm's ability to prevent a core hypothermia in the presence of a cooling load depends on a neural integration which activates peripheral thermogenic processes with nerve impulses from the hypothalamus. This hypothalamic thermogenesis outflow can be activated and driven by chilling the body shell (peripheral receptors) or by chilling the brain (central receptors). To what extent and under what circumstances 'peripherally' or 'centrally' driven thermogenesis is respectively utilized in the intact and unanesthetized animal has always been and continues to be difficult to ascertain. The question is raised as to whether hypophysial or adrenal activations are directly associated with neurologically elicited, cold-stimulated thermogenesis. It is recognized that the activity of these organs is recruited when there is need for body tissue to be converted to available fuel for thermogenic purposes. Thus, in the absence of an adequate food intake the activity of these organs would be indirectly recruited; the need for gluconeogenesis would be the specific hypophysial-adrenocortical activating stimulus, not cold as such.

[1] This paper constitutes a summary of the following publication: Neurologically Induced Physiological Resistance to Hypothermia. Hypothermia. (*Ann. New York Acad. Sc.* 20: 457, 1959.) The reader is advised to consult the original paper for illustrations and literature references.

ABILITY OF THE HOMEOTHERM to prevent a lowering of its core temperature in the presence of a cooling load is dependent upon a neural integration which activates the peripheral effector organs through efferent nerve impulses from the hypothalamus. These hypothalamic

efferented impulses are predominantly those which activate peripheral thermogenic processes.

The role of the hypothalamus in the realm of heat conservation is of lesser consequence because cutaneous vasoconstrictor responses can be efferented from the medulla. This is evidenced by the following observations. First, hemisection of the midbrain or pons does not cause a unilateral vasodilation (Horner's syndrome) and complete transection of the midbrain or pons does not produce generalized vasodilation. Secondly, when core temperature is raised in an unoperated animal by overheating, the cutaneous vessels dilate maximally and, on removal from the heating load, remain dilated until core temperature has returned to normal. In the midbrain preparation overheating dilates the cutaneous vessels as in the intact animal; however, on removal from the incubator the cutaneous vessels constrict rapidly before there is any lowering in core temperature. Thus the rate of body cooling is slower in the overheated midbrain preparation than in the overheated unoperated animal. Thirdly, Hardy and Hammel inform me that the posterior hypothalamectomized dog, inflicted with a striking deficit in its ability to resist cold exposure, does not display any deficit in heat conservation as determined by direct calorimetry.

PROBLEM AREAS PERTAINING TO COLD-STIMULATED THERMOGENESIS

There are two general problem areas associated with answering the 'what's' and the 'how's' of cold-stimulated thermogenesis. One pertains to filling in the details of the actual mechanics employed by the nervous system for activating and integrating cold-induced thermogenic processes. The other pertains to *1*) the identification of organs which are utilized specifically for cold-stimulated heat-producing purposes and *2*) the elucidation of the process whereby heat is liberated in each thermogenic organ.

Identification of cold-activated thermogenic organs. In the problem area of identifying organs that are utilized for thermogenic purposes, we have concerned ourselves with the question as to whether cold exposure elicits immediate endocrine responses and, if so, whether such responses are of any practical significance in physiological resistance to cold.

The approach to this problem was that of comparing the tolerances of hypophysectomized, adrenalectomized and unoperated dogs to standard cooling loads.

It was found that hypophysectomized and adrenalectomized dogs tolerate living in air temperatures of 3° and −20°C just as well as unoperated dogs, providing hypoglycemic symptomatology is not allowed to develop. If hypoglycemic symptomatology occurs, core temperatures begin falling and progress rapidly. If symptomatology is allowed to persist for some time, adrenal insufficiency crises develop and death supervenes unless vigorous adrenal cortical substitution therapy is instituted. If hypoglycemic symptomatology is avoided, there is no tendency to a core hypothermia or an adrenal insufficiency crisis.

These observations raised the question as to whether hypophysial and adrenal activations are directly associated with the sequence of physiological responses that collectively prevent a core hypothermia from occurring during acute exposure to moderate cooling loads. It is known, of course, that the activity of these organs are indirectly recruited, if there is need for body tissue to be converted (gluconeogenesis is a known example) to available fuel for thermogenic purposes. The need for gluconeogenesis is the specific hypophysial-adrenocortical activating stimulus, not cold as such.

There is the remote possibility that normally these endocrine organs are directly utilized and in their absence, as above, resistance-to-cold needs are adequately met by reserve and/or compensatory mechanisms. Also to be emphasized is that the foregoing observations are limited to acute exposure, and conclusions drawn and questions raised do not extend to the cold-acclimatized state.

Detailed mechanics of the neural integration. In the problem area of elucidating the mechanics of the central nervous integration of cold-stimulated thermogenic processes, there has long been good reason for supposing that the hypothalamic thermogenic outflow can be activated and driven in either of two ways, by chilling body tissues lying peripheral to the brain, or by chilling the brain.

There would seem to be no question about the existence of cold receptors located in body-shell tissues which have synaptic (reflex) connections with the hypothalamic thermogenic outflow. This conclusion is based on the fact that under several circumstances physiological resistance to cooling can be fully activated when the body core temperature (including brain) is slightly hyperthermic and the body shell is chilled.

Whether there are cold receptors located in the deeper peripheral body tissues which have similar reflex connections and functions remains largely an open question. Information about the circumstances under which the resistance-to-cooling outflow can be reflexly inhibited is also limited.

The existence of cold receptors in the brain has long been assumed on the basis of strong presumptive evidence. This evidence has been obtained by carotid blood cooling and local brain-cooling experiments. The existence of cold receptive elements in the brain has also been questioned on the basis of failures to obtain responses when parts of the brain were cooled.

Perhaps the most convincing evidence that the resistance-to-cooling outflow can be activated and driven by cold sensitive brain elements, as originally and continually suspected, is inherent in our observations on the isolated pyramidal bundles preparation. In this preparation the brain stem is completely transected through the lower pons except for sparing the pyramidal bundles.

Although there has been some variability in the preparations observed, nevertheless, they have all exhibited *1*) a near-normal resistance to cooling and *2*) a re-

markably consistent overshooting of core temperature during or immediately following removal from moderately heavy cooling loads.

These experiments would seem to be proof positive that the hypothalamic thermogenesis outflow can be activated and driven by cold-sensitive elements localized in the brain, i.e. without assistance from afferent influx from peripheral receptors. This is true provided afferent fibers subserving thermal reflexes do not course cephalad in the unsevered pyramidal bundles or enter the brain through the intact trunks of the first, second and third cranial nerves. These are the only routes whereby afferent impulses elicited from peripheral cold receptors could enter the brain. These possibilities seem remote, but nevertheless must be investigated.

The characteristic rise in core temperature to 40°C and even to 41°C before plateauing, during and subsequent to moderately heavy cooling loads in these preparations, has intrigued us no end. We wonder if perhaps this feature might afford an insight into the detailed mechanics of the neural integration. Assuming that the resistance-to-hypothermia outflow is completely deafferented in the isolated pyramidal preparation, this characteristic overshooting would be compatible with the following interpretation. Normally the resistance-to-hypothermia outflow is activated either reflexly or by cold-sensitive brain receptors or a potentiating combination of both, depending upon the particular situation at the time of onset of the cooling load. Once activated, this outflow continues to discharge until it is actively inhibited. In the absence of inhibiting afferents from the periphery, core temperature rises to the neighborhood of 40° to 41°C, at which point the outflow is reciprocally inhibited since the heat dissipation outflow is activated when blood temperature reaches the threshold for the heat sensitive brain receptors.

It seems, therefore, that there is every reason to continue—with the old-timers—to suppose that the resistance-to-cooling outflow can be activated and driven by cold-sensitive receptors located in the brain as well as by cold receptors lying peripheral to the brain. The location of the cold-receptive elements in the brain and the structural and functional characterization of these elements remain to be elucidated.

The sensory receptor organ and quantitative mechanism of human temperature control in warm environment

T. H. BENZINGER

Naval Medical Research Institute, National Naval Medical Center, Bethesda, Maryland

BENZINGER, T. H. *The sensory receptor organ and quantitative mechanism of human temperature control in warm environment.* Fed. Proc. 19, Suppl. No. 5: 32–41. 1960.—In widely varied warm environments and at widely varied levels of activity, responses and stimuli of human physical heat regulation were measured by gradient calorimetry and by cranial observations of internal body temperature. The inadequacy of rectal measurements was demonstrated. By forced dissociation of cutaneous from internal temperatures, by gradient calorimetric recordings of sweating and peripheral blood flow, with simultaneous recordings of the temperature stimulus at or near the two thermoreceptor sites, skin and internal cranial, in hot, warm, comfortable or cold environments, at low (20) or high (70 cal/sec) metabolic rates, proof was obtained that warm impulses from skin thermoreceptors do not participate in the central neural temperature regulation of man by sweating, and most likely not in such control by vasodilatation. The role of anterior hypothalamic heat center as terminal sensory organ with first neurons for these functions is discussed.

AN APOLOGY IS OFFERED for introducing the topic of hot environment into a symposium on cold acclimation. Although in Max Rubner's definition, the effector mechanisms of temperature control in warm environment are physical and those concerned with cold environment are mainly chemical or metabolic, the sensory and central components of the two mechanisms may have at least some common characteristics. Therefore, whatever may be learned of the neural mechanisms of physical heat regulation should be of interest in planning experiments on chemical temperature control in cold environment.

The purpose of this paper is to acquaint the members of the group with certain experimental evidence concerning sweating and cutaneous vasodilation (1). It has been possible to demonstrate that these responses are inseparably connected with, and uniquely related to, the stimulus of

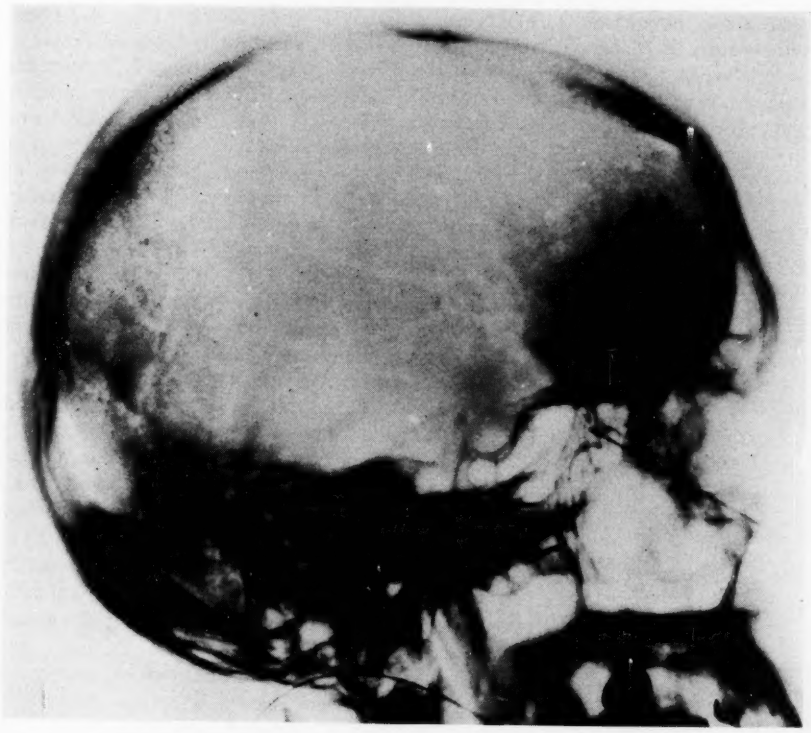


FIG. 1. Cranial temperature measurement. A thermoelectric probe is shown by x-ray at the anterior wall of the sphenoid sinus.

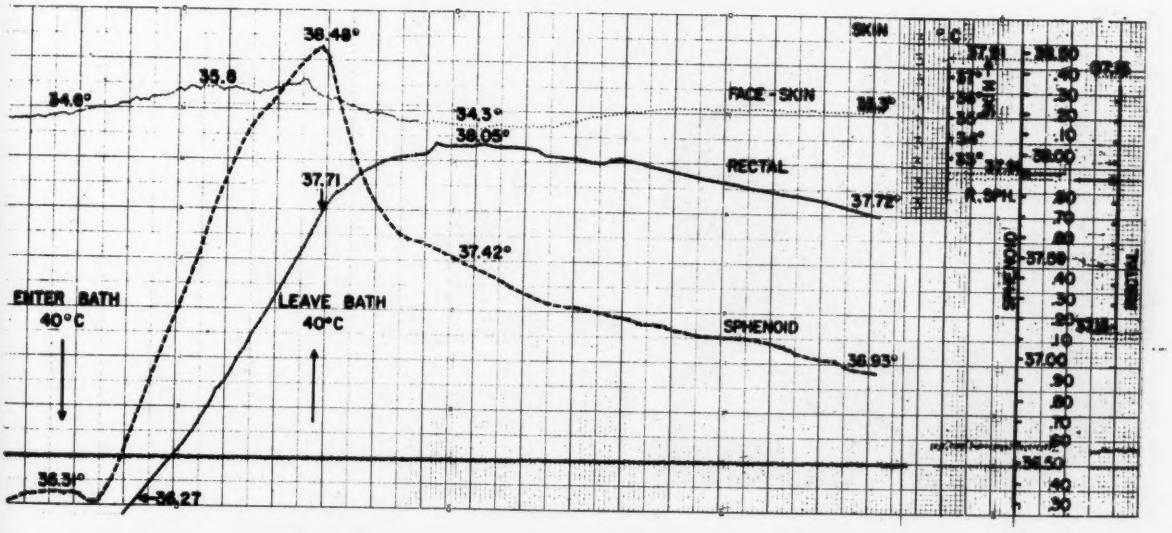


FIG. 2. Deviations of rectal temperature from cranial temperature upon entering and leaving a bath of 40°C. The rising internal cranial temperature is poorly reflected in the rectal measurement. A difference of −0.8°C resulted which was reversed to a +0.7° difference after leaving the bath. These differences are several times the range of physiological control in warm environment.

increased cranial internal temperature. Every increase of cranial internal temperature by 0.01 °C was answered with 0.7–1.5 cal/sec. of sweat evaporation and with 0.25–0.50 ml/sec. of additional cutaneous blood flow. The relation was nearly linear. The threshold for the two responses, or, in other words, the 'setpoint' of the human internal thermostat, was found to be sharply defined, 36.9°C in the one individual thus far most thoroughly investigated. It was found anywhere between 36.5 and 36.9°C in seven other subjects (the seven astronauts).

After this introduction and summary, which is ob-

viously at variance with some conclusions though not with any experiments of classical temperature physiology on the subject, it is first necessary to show how cranial internal temperature may be measured, and why the usual measurement of rectal temperature principal technique of classical temperature physiology—could not possibly uncover these facts.

For the skull x-ray (fig. 1), the surgeon, G. W. Taylor, placed a copper-constantan thermocouple at the mucosa of the anterior outer wall of the sphenoid sinus of an investigator. (This area is supplied with blood from the internal carotid artery.) The nostrils were occluded.

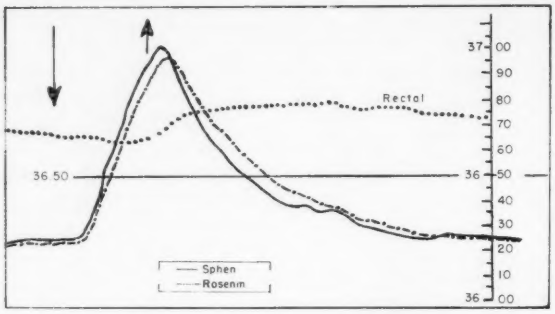


FIG. 3. Deviation of rectal temperature from cranial temperature upon warming both arms in water of 40°C. The abrupt rise and fall in cranial temperature is not reflected in the rectal measurement.

The thermocouple was worn for more than seven hours, and simultaneous recordings were taken of rectal and 'sphenoid' temperatures under a variety of experimental conditions. Figure 2 shows the effect of a warm bath, such as Burton and Bazett have used in their classical work, from which it was concluded that there existed no reproducible relation between cutaneous blood flow and 'internal' body temperature. The figure shows that it is not permissible to substitute rectal for 'hypothalamic' temperature. There are deviations of $+0.7°$ and $-0.8°$, a total of 1.5°C, between the rectal and sphenoid measurements. Similar discrepancies may be observed upon putting both arms into warm water (fig. 3), or upon cooling internal body temperature by oral ingestion of 450 grams of sherbet ice (fig. 4). The differences between rectal and cranial temperatures may be three times larger than the entire physiological range of control.

On the other hand, it can be demonstrated that cranial measurements of temperature taken at various sites in the area of the internal carotid artery—from which the hypothalamus is supplied—are consistent with one another, regardless of location, differences in metabolic activity, and drastic changes of the experimental conditions. For the experiment of figure 5, thermocouples were placed:

1) At the tympanic membrane, that is, close to the internal carotid artery where it winds through the petrous part of the temporal bone.

2) At the mucosa in the anterior ethmoidal region,

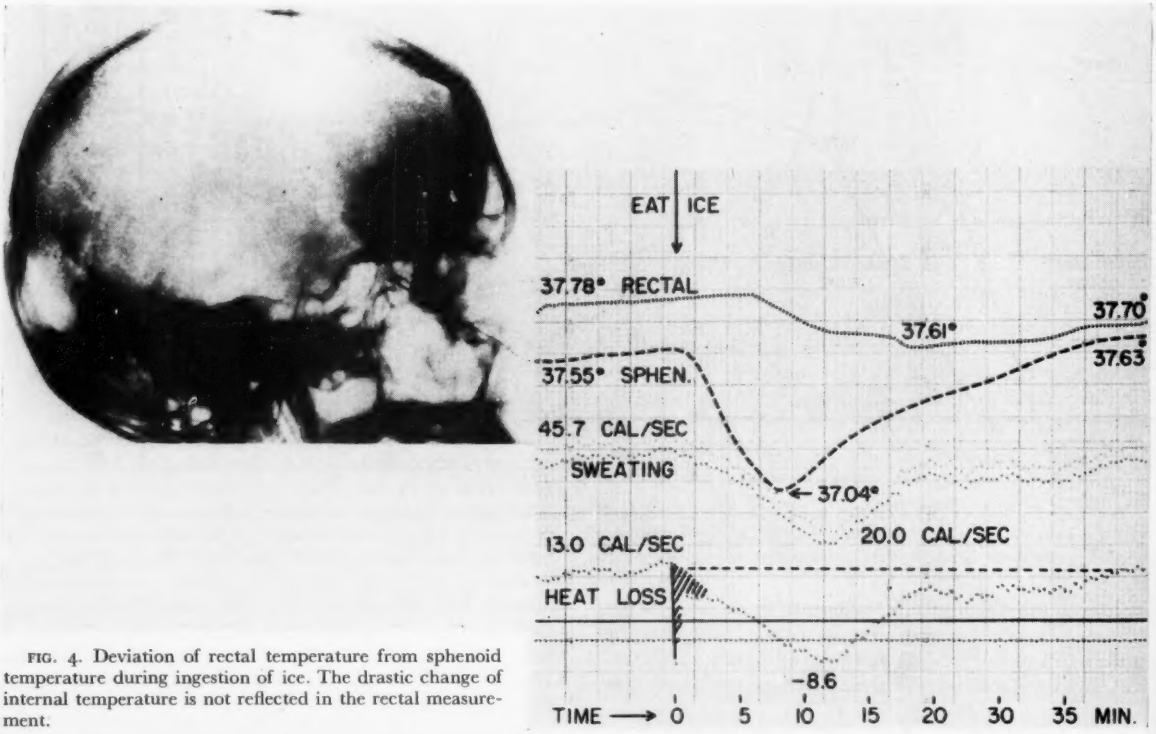


FIG. 4. Deviation of rectal temperature from sphenoid temperature during ingestion of ice. The drastic change of internal temperature is not reflected in the rectal measurement.

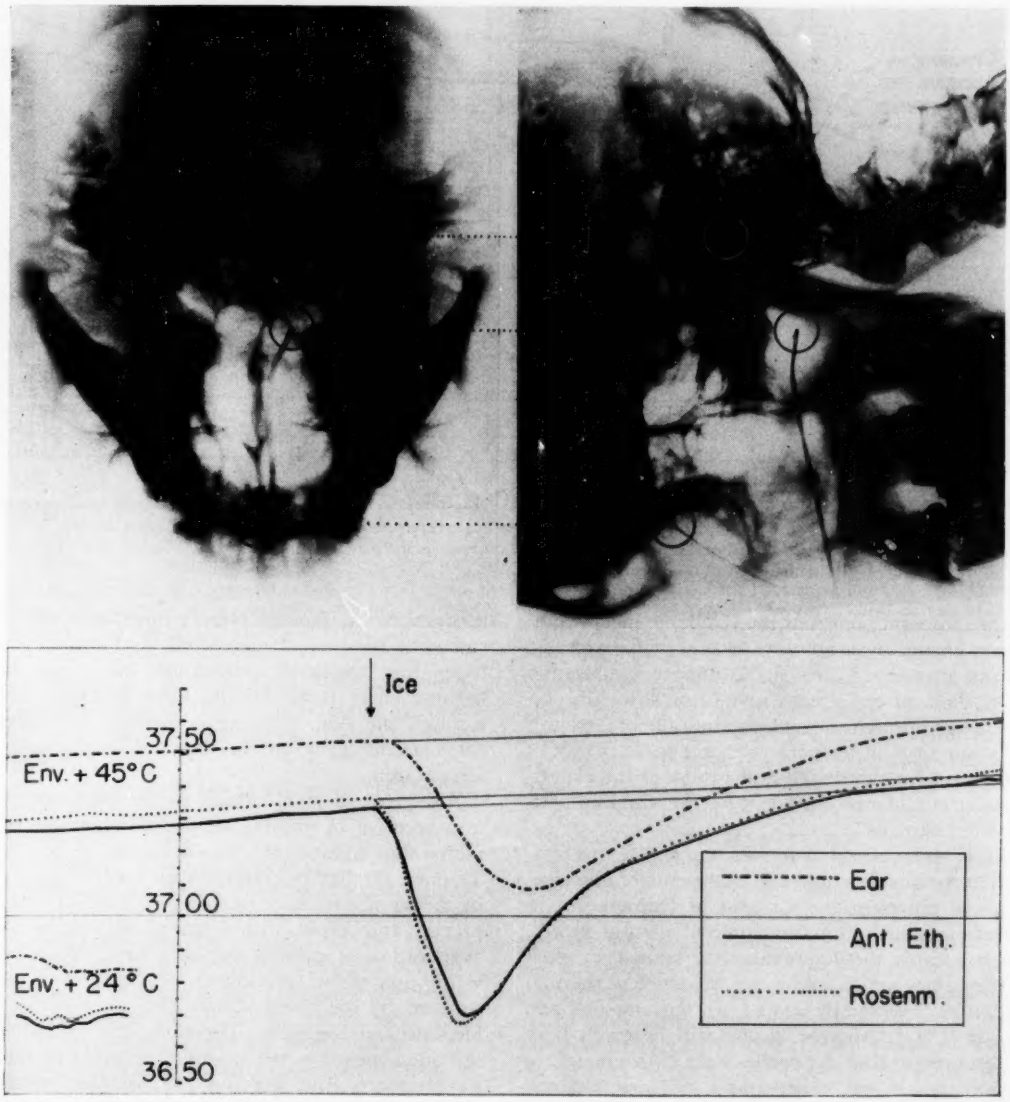


FIG. 5. Recordings of internal cranial temperatures from three different sites. Thermocouples for measuring cranial temperatures were applied to the anterior ethmoidal region, to the nasopharyngeal recess and to the tympanic membrane. Temperature recordings follow a close pattern after thermal stimulation by ingestion of ice. The slightly slower response at the tympanic membrane is due to the poorer conduction in this air space compared with the other sites on mucous membranes and to the poorer circulation in the bone.

supplied from the ophthalmic artery, a branch of the internal carotid.

3) In the depth of the nasopharyngeal recess of Rosenmueller, only a few millimeters from the stem of the internal carotid artery.

From these three distant sites, simultaneous and continuous measurements were obtained as shown in figure 5 and, more extensively, in figure 6. The subject was first transferred from an environment of +24°C into an environment of +45°C. Later on, a drastic reduction of internal cranial temperature was brought about by rapidly swallowing 450 grams of sherbet ice. These experimental procedures resulted in wide and rapid changes of the temperatures as measured. Nevertheless, the measurements taken at the three different places show for all practical purposes the same time course. The only major differences are a slower response (without quantitative differences in the changes observed) for the measurement at the tympanic membrane, and a parallel shift by approximately 0.2°C of the tympanic observation. The reason for the slow response is obviously a relatively poor circulation of blood through the petrous

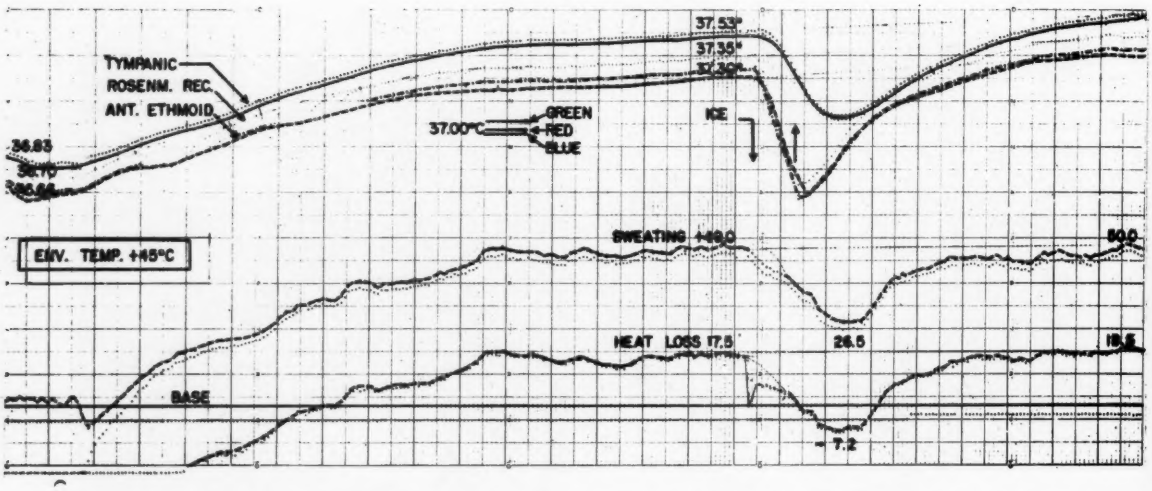


FIG. 6. Recordings of internal temperatures from various cranial sites. In spite of drastic changes of environment (25° to 45°C at the beginning of the recording) and of internal temperature (after ingestion of ½ kg of ice), the temperatures at distant sites move essentially in parallel. The recording from the eardrum has a slower response and a temperature higher by 0.2°C for reasons given in the legend to fig. 5.

part of the temporal bone and the tympanic membrane. The reason for the lower absolute level of temperature at the mucous membrane sites is the minute evaporative cooling of these places, a consequence of slow diffusion of water vapor through the choanae into the oral cavity. (The absolute level of temperature, or a parallel shift of it, is irrelevant for the design and results of the experiments under consideration, except for the absolute position of the 'setpoint.')

From the observations of figures 5 and 6 it was concluded that the changes observed at the sites of measurement closely represent the changes of temperature in other areas supplied from the internal carotid artery. One such area is the hypothalamus, known to elicit thermoregulatory action under the influence of thermal stimulation as observed by Kahn (1a), Barbour (2), and Magoun *et al.* (3). Another reason will be given later for the assumption that the probes were close enough to the hypothalamus for observations of hypothalamic temperature.

In summary, sites and techniques have been found, or prepared, to measure, in a study of the mechanisms of human temperature control, one of the potential stimuli, cranial internal temperature. The other potential stimulus, average skin temperature, was measured in ten selected places and integrated by serial wiring. Space does not permit a description of the details of the technique, which was not far from conventional. It may, however, be of interest that it was possible to confirm the measurements of skin temperature with calorimetric observations. Under conditions where skin temperature is identical with wall and air temperatures in a calorimeter, the total of radiated, conducted and convected heat losses (not including evaporative heat loss) must be zero. Secondly, under conditions where skin temperature is identical with internal body temperature, the total of radiated, conducted, convected, and evaporative heat losses (not including pulmonary loss) must be zero, because there is no driving force initiating heat flow through the skin. This again permits an independent calorimetric check on the direct measurements of skin temperature.

After this short discussion of the techniques for the measurement of stimuli, the measurements of the vasomotor and sudomotor responses need to be described. The new method of gradient calorimetry (4, 5) permits, by means of a ventilatory circuit, the direct, continuous, precise and rapid measurement of cutaneous water evaporation in calories per unit time. With adequate ventilation of the calorimeter, evaporation of the water secreted by the sweat glands of a nude subject is immediate and complete. Therefore, the calorimetric observation measures the intensity of sweat gland action. Furthermore, the gradient calorimeter permits the measurement of total heat transfer through the skin. From this and from internal and cutaneous temperatures, the index of cutaneous blood flow, thermal conductance (6) is readily derived.

Even with methods for the simultaneous, continuous, and rapid measurement of both the stimuli and the responses it would still not seem possible to discover the quantitative mechanism of human temperature control. In addition, specific experimental conditions must be met in order to obtain conclusive, unequivocal answers to the question of whether cutaneous or cranial internal temperature, or both or neither, are the physiological stimuli for the responses of sweating and cutaneous vasodilation. For, normally, the temperatures of skin and brain are moving jointly up and down together, reflecting the environmental changes; in other words,

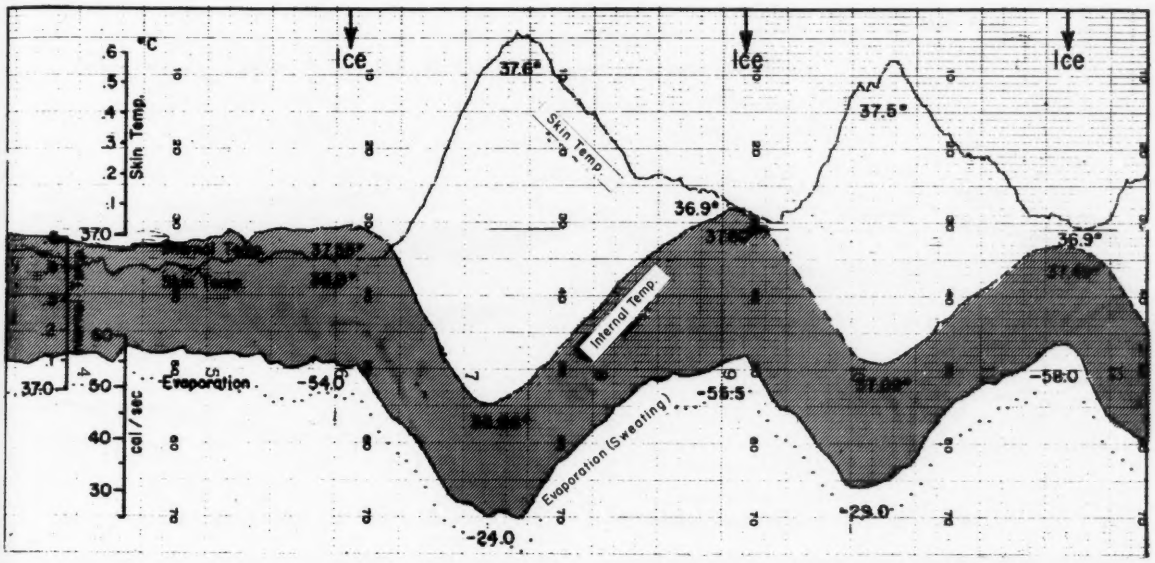


FIG. 7. Sweat gland activity (evaporation), a response to internal, not skin, temperature. By repeated oral ingestion of ice, cranial temperature and skin temperature were driven in opposite directions. Rate of sweating followed internal, cranial temperature, not skin temperature. The paradoxical pattern of skin temperature was caused by cessation of sweating after ingestion of ice.

the two are often linked in a relationship which is coincidental. This coincidental, deceiving relationship must be broken if the experiments are to permit reliable conclusions.

In the present study, two simple methods were applied for separately influencing internal and cutaneous body temperatures, and for sometimes driving the two in opposite directions: *1*) Oral ingestion of substantial quantities of sherbet ice has the peculiar effect of cooling internal temperature while, under the conditions of the experiments, it raises skin temperature on the face as well as over the rest of the body. *2*) Muscular activity, as it raises internal heat production, increases greatly the internal cranial temperature whereas it influences only moderately the temperature of the human skin.

Two kinds of experiments were carried out with these methods: *a*) During rapid changes in a transient state, continuous recordings were obtained to show whether the responses of sweating and vasodilation follow the stimulus of skin temperature or of hypothalamic temperature, when the two are moving in opposite directions. This method has the advantage that it must reveal instantaneous and possibly transient phenomena. *b*) Steady-state measurements were taken of sweat rates, conductance, and cutaneous and cranial temperatures for obtaining a quantitative picture of the mechanism.

A typical observation of the first kind is shown in figure 7. Three times, the cranial internal temperature was lowered drastically by rapid oral ingestion of 450 grams of sherbet ice. The rate of water evaporation—or intensity of sweat gland action—as a response followed like an image the recording of cranial internal temperature as a stimulus. The integrated total of skin temperature moved in the opposite direction. The reason for this latter phenomenon was physical, not physiological: while the reduced hypothalamic temperature caused the reduction in the rate of sweating, the drying skin was heated in the intensely hot environment of 45°C by radiation, conduction and convection. Whereas in the experiment just described, internal temperature was artificially upset and separated from its relation with cutaneous temperature, the converse was done in the experiment of figure 8.

In the hot environment of +45°C the skin of the face —where roughly one-half of the total of cutaneous thermoreceptors are believed to be concentrated—was cooled with an ice mask suddenly from 37.5° to a final temperature of 31.5°C. If skin temperature were a major stimulus for sweat gland action, it would be expected that the rate of sweating would drop immediately and soon reach zero upon sudden cooling to such a low temperature (skin temperature in figure 8 was recorded with $\frac{1}{10}$ of the sensitivity of the internal temperature recording). However, no sudden drop is visible in the rate of sweating. Only a shallow depression by 15 cal/sec. is observed, which is a close reflection of a shallow depression in the record of cranial internal temperature by 0.15°C. The conclusion is that the well-known cessation of sweating as a result of face cooling is not elicited by skin thermoreception. It is a consequence of reduced cranial internal temperature. The latter is a result of counterflow cooling in the ascendant blood of the carotid artery by contact with cool blood descending through the jugular vein from the cooled skin of the face. This mechanism, for extremities, has been ably described by Bazett *et al.* (7).

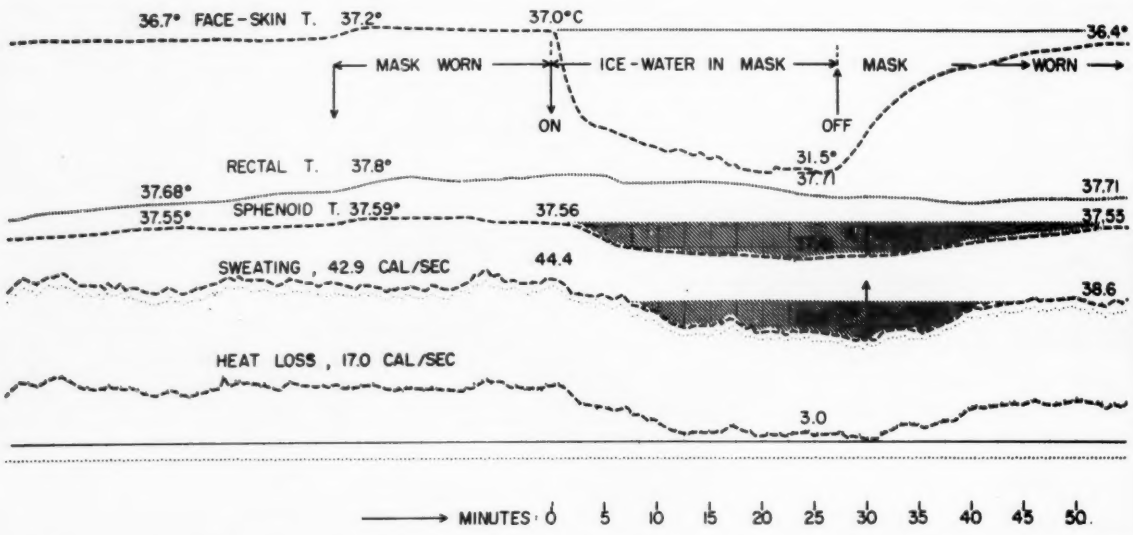


FIG. 8. Stimulation of skin thermoreceptors on the face. Sudden and drastic cooling of the face from 37°C to 31.5°C did not result in cessation of sweat gland activity. The depression of sweating by cal/sec. was caused by a simultaneous depression of cranial temperature due to the exchange of heat between the cool jugular veins and the carotid blood.

Conductances as indices of the rate of peripheral circulation were computed for figure 7 from the cutaneous and internal temperatures and from the heat loss through the skin, simultaneously recorded though not shown in the figure. Conductances at the peaks of internal temperatures were found to be three times as high compared to the conductance values at the minima of internal temperature. Although precision cannot be claimed for measurements of conductance in nonsteady states, it became obvious from these observations that both sudomotor and vasomotor activities responded to internal, not cutaneous thermoreception. With simultaneous and rapid recordings of the essential quantities it thus became quite improbable, after a single experiment, that the thermoreceptors of the skin participate at all in human physical heat regulation by sudomotor and vasomotor activity. In view of the importance of the issue it was felt, however, that tests should be extended over the full range of human physical heat regulation, to rule out any influence of skin temperature on sudomotor activity, to study peripheral blood flow in a similar way, and to arrive at a quantitative analysis of the mechanism of physical heat regulation in man. Experience showed that ultimate precision and reproducibility can only be attained in steady states, where the heat flow rate is uniform throughout the system, and differences of temperature are observed only in space, not in time.

With this intention, one individual was taken nude in numerous experiments through eight different environments, ranging from cold (+10°C) to very hot (+45°C) in the calorimeter. In each of these experiments steady states were established—with respect to the stimuli and responses—by waiting an hour or more at each of three different rates of metabolic heat production: rest (20 cal/sec.), moderate exercise (45 cal/sec.), and strenuous exercise (70 cal/sec.). This covers the majority of physiological conditions usually experienced in everyday life (considering that wide changes of environment are usually offset by adequate clothing, shelter, rest, or movements). It was obvious that any coincidental relationship between cutaneous and internal temperature must have been broken in such a series, for during strenuous exercise in cold environment the subject had a cold skin and warm interior and in hot environment at rest, internal temperatures were moderate and skin temperatures were very high. Therefore, if classical theory were correct, that both internal and cutaneous temperatures were stimuli for the hypothalamic excitation of sweat glands and cutaneous vessels, no reproducible relationship could possibly be shown between either cutaneous or internal temperature as stimuli and the vasomotor and sudomotor responses for all the observations in this series of experiments. For, whatever reproducible relationship existed between a response and one of the two stimuli must have been broken by the variations forced upon the other stimulus, which would be similarly effective. For plots of sweating rate against the stimulus of skin temperature and the stimulus of cranial internal temperature, the following characteristics could be predicted:

a) Under no circumstances will, in both of the plots, the responses observed at different metabolic rates and internal temperatures fall upon one best line, within experimental errors. Either one of the plots, or both of them, will appear senseless and disrupted.

b) If, as Bazett or Kerslake have assumed, the thermoregulatory responses were elicited by deep skin re-

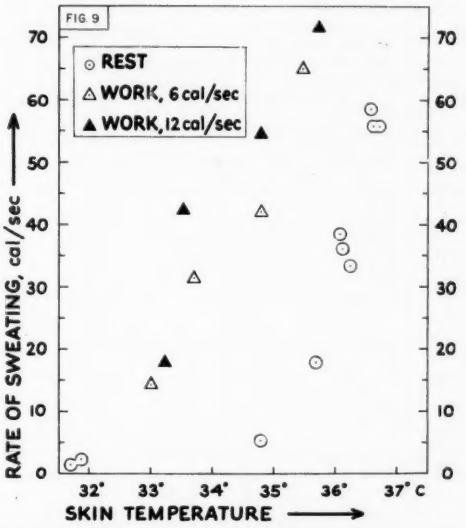


FIG. 9. Rates of sweating plotted against skin temperature. Under widely varied conditions of environmental temperature (10° to 45°C) and internal heat production (by exercise) no reproducible relation was found between skin temperatures and sweat gland activity. The influence of internal temperature (high in the working man and low when resting) is obvious from this disrupted plot.

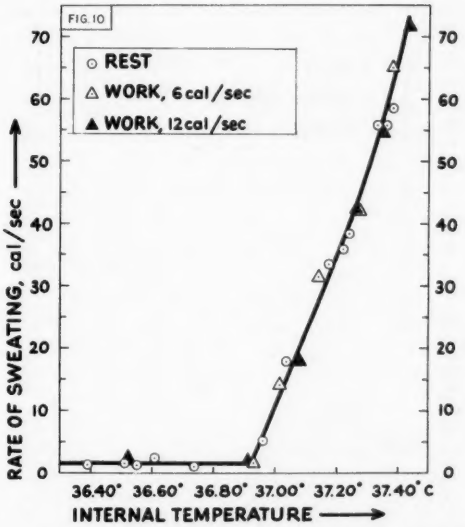


FIG. 10. Rates of sweating plotted against cranial temperature. In contrast to skin temperature, cranial temperature as a stimulus is inseparably linked to sweat gland action, the regulatory response. The influence of skin temperature is zero. (Working and resting observations coincide). The sweat glands respond with 1 cal/sec. of sweat (evaporative cooling) to each 0.01° increase of internal cranial temperature.

ceptors (intermediate between cutaneous and internal) or by gradients of temperature between two sets of thermoceptors, one deep, one superficially located, and therefore neither skin temperature nor internal temperature were the true stimulus, both plots will appear disrupted and senseless. Disruption in both plots would also be expected in case of participation of thermoreceptors in muscle, which would be heated during exercise.

c) If, as the majority of physiologists assume, the responses were elicited by both internal and cutaneous influences of temperature, both plots will appear disrupted, for whatever relationship existed with one of the two stimuli would be disrupted by the wide variations of the other, artificially introduced with the experimental technique described.

d) If the relationship between cutaneous and internal thermoregulatory stimulation were 50:50, the degree of disruption will be the same in both plots. If, however, one of the stimuli were predominant, the degree of disruption will be higher in the plot against the 'weaker' stimulus, and lower in the plot against the 'stronger' stimulus.

e) One smooth plot (that is, a plot in which all deviations would be within the combined experimental errors of all the methods of measurement) will only be obtained if one of the potential stimuli has no influence whatever on the regulation of temperature by means of the responses under consideration.

f) If this phenomenon should unexpectedly be observed, it is unthinkable that it would have been brought about by errors of measurement, or by uncontrollable factors in the experimental situation. Such errors or factors could only disrupt an existing unique relation between the response and one of the stimuli. They could never simulate or create it.

The experimental answer to the argument as proposed was unequivocal. The 'skin-plot' (fig. 9) was disrupted. The 'internal temperature-plot' (fig. 10) was smooth within experimental errors. The influence of skin temperature—and consequently skin thermoceptors—upon sweat gland activity was therefore zero. Internal cranial temperature and the response of sweating were found to be inseparably and almost linearly related. Increase in cranial temperature by 0.01 °C was answered by sweating in the order of 1 cal/sec. The threshold of the response (setpoint of the human thermostat) was sharply defined. Below the threshold the sweat glands were inactive.

Similar statements may be derived from the plots obtained with vasomotor response against the stimuli of cutaneous and cranial internal temperatures (figs. 11 and 12). In principle, vasodilation, like sweating in a warm environment, was found to be a response to an increase of cranial internal temperature beyond the threshold already observed with sudomotor action. There is, however, one important difference: Whereas for sudomotor action the influence of skin temperature was zero, a significant influence of skin temperature (not skin-thermoreception!) was visible in cutaneous vasodilation.

For an explanation of the discrepancy between working and resting observations in figure 12, several influences of temperature upon cutaneous vessels are known

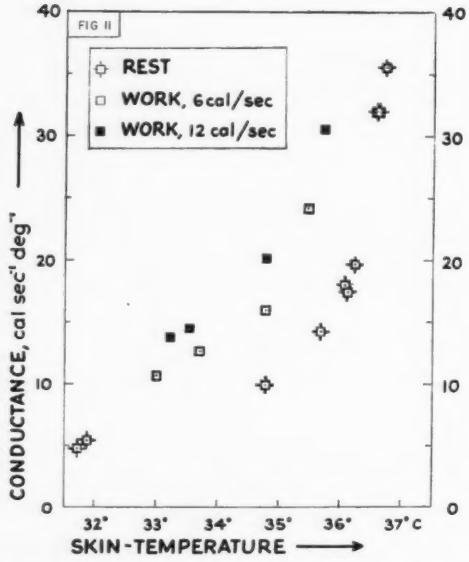


FIG. 11. Vasomotor response plotted against skin temperature. Calorimetrically, the rate of blood flow was determined and plotted against skin temperatures. No reproducible relation was found. In the working man, skin circulation increases in spite of low skin temperatures.

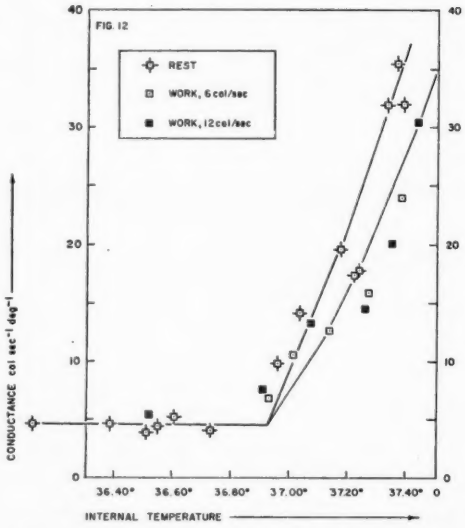


FIG. 12. Rate of blood flow through the skin plotted against cranial temperature. Peripheral blood flow, like sweat gland activity, is a response to internal cranial temperature. However, skin temperature also influences the cutaneous circulation directly after transection of the nerves (as others have shown). This influence is visible in the downward shift of the rate of cutaneous circulation during exercise when, at a given internal temperature, the skin temperature is lower than at rest, due to the higher convective and evaporative cooling.

and well established through the observations of others:

a) a direct effect of temperature upon smooth muscle;

b) neurochemically mediated action;

c) axon reflexes;

d) spinal reflexes originating and terminating in vessels of the same segment, cutaneous or visceral.

Actions *a*), *b*) and *c*) do not require participation of a nervous system, since they have been observed after transection of the cutaneous nerves. Effect *d*) does not require thermoreceptors, since it is absent after thermal stimulation that does not result in a vascular response at the site of the stimulus, as described by Kuntz (8). Certainly, effect *d*) as a spinal reflex does not require participation of the hypothalamus.

CONCLUSIONS

A quantitative analysis of the human autonomic central mechanism of heat regulation in warm environment may be given as follows. As Rubner found in 1900, the environmental impediment to loss of heat through the avenues of radiation and convection is compensated by increased evaporative heat loss, which balances the total losses with the magnitude of metabolic heat production. The two effector mechanisms responsible for this performance are the sweat glands and cutaneous vessels. As shown above, the sweat glands respond in a nearly linear fashion to increasing internal cranial temperature with approximately 1 cal/sec. to 0.01 °C above a sharply defined setpoint, the threshold near 37 °C.

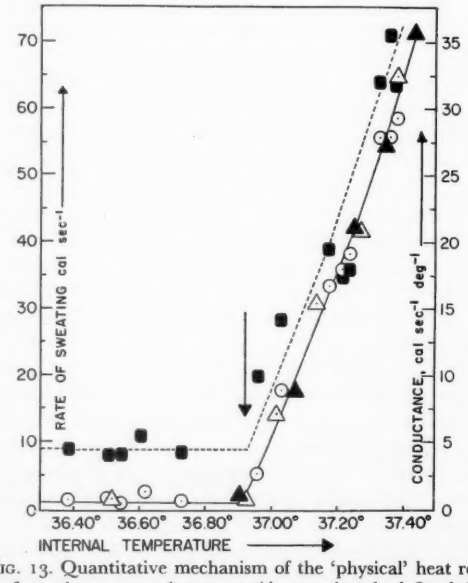

RATE OF SWEATING cal sec⁻¹
CONDUCTANCE, cal sec⁻¹ deg⁻¹
INTERNAL TEMPERATURE
36.40° 36.60° 36.80° 37.00° 37.20° 37.40°
0 10 20 30 40 50 60 70
0 5 10 15 20 25 30 35

FIG. 13. Quantitative mechanism of the 'physical' heat regulation of man in warm environment. Above a sharply defined threshold of cranial internal temperature, the low and constant rates of sweating and peripheral blood flow respond and rise in reproducible proportion with cranial internal temperature, the stimulus. In this individual the threshold was 36.9 °C and the responses were 1 cal/sec. of sweat evaporation, and 15 ml/min. of blood flow to every 0.01 °C of increased temperature. The result is lasting homeostasis, with only insignificant increase of internal temperature.

Heat is conveyed from the interior of the body to the skin for subsequent dissipation through an increase of peripheral blood flow of approximately 0.25 ml/sec. in response to an increase of 0.01°C. (fig. 13). The concerted action of the two responses in their 'tandem' arrangement maintains internal temperature against both internal and external heat stress within narrow limits. No other mechanisms are required to explain the regulation of human body temperature in warm environment in a quantitative manner, since steady states of homeostasis had been atttained in the experiments.

A number of other conclusions follow from the experimental facts presented:

a) It appears implicit from the present findings that the central temperature-sensitive structures identified with warm stimulation by Barbour (2), Magoun *et al.* (3), Hemingway (9) and Freeman (10), are lacking cutaneous thermoreceptive impulses adequate for the production of powerful, accurate and sustained responses of the sweat glands. For if such impulses were arriving at the central effector neurons for sweating, their influence would have been uncovered with our methods of measurement, under the conditions of the experiments. Therefore, unless the rather remote alternative is entertained, that other peripheral, though certainly not cutaneous, and internal, though not necessarily cerebral, warm-receptors are responsible, the task of receiving the stimulus is left to the anterior hypothalamic site, which has been shown to elicit the responses. This site would therefore have to be considered a terminal sensory receptor organ with first neurons for temperature, comparable to the retina with its first neurons for light, and not a synaptic 'center' in which impulses from the skin are modified by the central level of temperature.

b) The evidence is negative for direct neural pathways connecting the warm receptors of the skin via thalamus with the hypothalamus.

c) The sense of temperature in the human skin does not have one principal function previously ascribed to it: to serve as the source of the sensory, afferent warm impulses for temperature control by sweat glands and cutaneous vessels.

While the experiments described (cf. also (1)) are consistent with an absence of skin-thermoreceptor warm-impulses to cutaneous vessels, it is appropriate to stress the importance of skin thermoreception in other mechanisms of human temperature control. Thus skin thermoreception dominates the 'Pavlovian' mechanism of control by conscious sensations and willful actions (locomotion, changes of posture, use of clothing, sheltering, bedding, warm and cold water and the like). Skin thermoreceptors are also the origin of cold impulses to the differently organized, somatic reaction of man to cold.

Gratitude is expressed to Charlotte Kitzinger, M.D., who, with the author, developed the method of gradient calorimetry with the generous support, since 1947, of the Naval Medical Research Institute and the Bureau of Medicine and Surgery. This method was the basis of the work presented. G. W. Taylor, Commander, MC, USN, United States Naval Hospital, Bethesda, Maryland, has carried out the surgical procedures which will be described in another publication.

REFERENCES

1. Benzinger, T. H. *Proc. Natl. Acad. Sci.* 45: 649, 1959.
1a. Kahn, R. H. *Arch. ges. Physiol.* 81, Suppl. 134, 1904.
2. Barbour, H. J. *Arch. exper. Path. u. Pharmakol.* 19: 1, 1912.
3. Magoun, H. W., F. Harrison, J. R. Brobeck and S. W. Ranson. *J. Neurophysiol.* 1: 101, 1938.
4. Benzinger, T. H. and C. Kitzinger. *Rev. Sci. Inst.* 20: 849, 1949.
5. Benzinger, T. H., R. G. Huebscher, D. Minard and C. Kitzinger. *J. Appl. Physiol.* 12: S1, 1958.
6. Burton, A. C. *J. Nutrition* 7: 497, 1934.
7. Bazett, H. C., L. Love, M. Newton, L. Eisenberg, R. Day and R. Foster. *J. Appl. Physiol.* 1: 3, 1948.
8. Kuntz, A. J. *J. Neurophysiol.* 8: 421, 1945.
9. Hemingway, A., T. Rasmussen, H. Wickoff and A. T. Rasmussen. *J. Neurophysiol.* 3: 329, 1940.
10. Freeman, W. J. and D. D. Davis. *Am. J. Physiol.* 197: 145, 1959.

Discussion

A. K. WEISS, T. H. BENZINGER, A. D. KELLER, S. A. D'ANGELO, O. G. EDHOLM, R. W. BRAUER, K. M. KNIGGE

Dr. Weiss: This is an international symposium and I think Dr. H. Hensel's work should be mentioned. Unfortunately, Dr. Hensel could not attend this meeting. As I recall it, his findings contradict those of Dr. Benzinger. I take no sides in this matter but wonder if you would care to make some comments on Dr. Hensel's work and how your findings relate to it.

Dr. Benzinger: I wish to say, Dr. Weiss, that only 10 days ago I had a most pleasant discussion, lasting several hours, with Dr. Hensel in Marburg, Germany, and that we have no disagreement at all in the experimental findings. Of course, he emphasized the fact that these observations cannot be extended without reservations to chemical regulations on the cold side,

which I have not implied, and I cannot see any other disagreement with any other experimental findings; whenever we are in disagreement with conclusions that have been drawn from measurements (as in Bazett's and Burton's studies on conductance), the difference is explained by the facts which I have had the privilege to show, differences such as deviations of rectal temperature, which was the basis of classical temperature physiology, from internal cranial temperature, which is the stimulus of human physical heat regulation.

DR. KELLER: I would like to ask Dr. Benzinger if perhaps he wouldn't allow that the results obtained, if he used radiant heat of sufficient intensity applied to localized parts of the body, might cause him to modify his conclusion.

DR. BENZINGER: Our experiment was carried out in a mild convection which was so distributed that it did not locally disturb, but which was enough to carry off the sweat, because, of course, dripping sweat would have always defeated our purpose; with regard to local stimulation of certain areas, we have done several experiments, of which I haven't time to give all the details, but one I shall be pleased to show: sudden cooling of the skin from 37° to 31.5°C with an ice mask in a hot environment does not result in a sudden reflex reduction or abolition of sweating. It results only in a shallow depression of sweating, a mirror image of the shallow depression in the recording of cranial internal temperature. Cooling by 0.01°C reduces sweating by 1 cal/sec. The reduction of the internal cranial temperature is caused by counterflow cooling of the carotid arterial blood through thermal contact with blood returning from the ice-cooled face through the jugular veins.

DR. KELLER: Your conclusions should be qualified to the extent of being limited to the conditions of your particular experiment.

DR. D'ANGELO: Dr. Keller's remarks about transection of pyramidal bundles and medial lemnisci made me curious about the sensitivity of the paralytic to cold. In the next presentation, Dr. Benzinger emphasized the lowered temperature of the blood itself as influencing the hypothalamus. It occurs to me that inasmuch as virtually all of the blood going to the hypophysis first passes through the hypothalamus it might be interesting to know whether cooled blood irrigating the pituitary has any effect on trophic mechanisms, irrespective of hypothalamic neurohumors.

DR. BENZINGER: This is certainly a very interesting topic I must admit, but I have had no personal experience with it and we have not yet directed our studies to these objectives.

DR. EDHOLM: I was very interested to hear that the temperature in the ear is considered to be so similar to the hypothalamic temperature. Some measurements have been made in my laboratory of aural temperature, and it was found that in cold environments the temperature within the external auditory canal followed very closely the mean skin temperature and was quite different from any other temperature measured. The thermocouples were not applied to the surface of the drum, a technique I admire but do not envy. I would like to ask Dr. Benzinger's opinion of aural temperature when carefully measured in relation to these other more vigorous measurements, because I would like to suggest that aural temperature is one not to be entirely despised.

DR. BENZINGER: In oral measurements there is the danger of evaporative cooling. It is very hard to bypass the entire oral cavity for respiration; consequently, it is safer, I believe, to measure in the nasal cavity, because we can block the nasal cavity at least to continuous transfer of air. Even so, it is difficult to block the choanae; we tried that, too, with a bag that was needled up to the base of the skull and then filled with ice water, but I do not want to go into these things now. With regard to ear temperatures, I think you are right in saying that they are dangerous; it has been mentioned today, I do not know in which one of the presentations, that cooling the carotid arteries also involves skin temperature. In other words, in the cold, when skin temperature goes down appreciably from normal levels, there is an influence on ear temperature and we cannot safely rely on it for measurement; so what I presented was restricted to moderate, warm and hot climates. There skin temperature is not changing as widely as in a cold environment, which makes the procedure safer. But as soon as we used an ice collar on the neck and so on, ear temperature no longer coincided with the other internal kinds of measurements I have shown.

DR. EDHOLM: We had hoped that the measurement of aural temperature would be a very convenient way of following deep body temperature in the field, but in cold environments this has not proved to be satisfactory.

DR. KELLER: The fact that some thermogenic fibers course with the pyramidal bundles does not necessarily indicate that all of them do. It is highly probable that selective severance of these bundles would not cause an appreciable deficit in regulation against cold.

DR. BENZINGER: Maybe I can make just one comment on what this may mean on the cold side. It could mean that whatever activity in shivering is elicited from the skin, it is not hypothalamic, but cortical.

DR. KELLER: I wish Dr. Benzinger would substitute the word 'brain' for 'hypothalamus' because there is no assurance that thermal receptors located in the brain are limited to, or even located in, the hypothalamus.

DR. BENZINGER: I admit that I don't know, but I was relying on the brilliant work of Ranson and Magoun who have studied this area; as far as I know, no other finely sensitive area has been found in the brain.

DR. BRAUER: Dr. Keller, if you recall, you commented on the immersion hypothermia, shivering after a short period of immersion. Now, this unquestionably occurs. I am not at all sure, however, if this should be interpreted as I believe Dr. Keller tried to interpret it, that is, as evidence of skin receptors. By far the most dramatic shivering one gets with immersion under any condition is not during the actual period of immersion, but during the rewarming, when blood begins to flow again through the cooled peripheral tissues and is allowed to return to the core; that seems to be the hypothesis that works best.

DR. KELLER: I appreciate that shivering may be more intense following immersion than during immersion, but I agree with Bazett's interpretations that there would be no possibility of brain temperature being lower than the colonic temperature under the circumstances he describes; accordingly, shivering would of necessity need to be driven by chilled receptors located in the body shell.

DR. KNIGGE: If Dr. Benzinger's technique could be applied to the larger experimental animals, it would be very interesting to record brain temperatures in this fashion before and after placement of discrete hypothalamic lesions. In this way, it might be possible accurately to localize thermosensitive areas.

DR. BENZINGER: I think there is really a field for neural analysis to verify: which are the thermoreceptor cells, where is the second neuron, and so on. One could probably make an analysis of the crista supra optica of the hypothalamus comparable to the analysis that has been made with the human retina. I would be most happy if somebody would be interested

in this problem; also, of course, in physiological studies by partial destruction and degeneration.

DR. D'ANGELO: So much stress has been placed on central neural mechanisms that it impels me to ask what I should tell my medical students when they inquire about the function of the sensory receptors of Ruffini and Krause.

DR. BENZINGER: I am very grateful for this question; this is something I could not take up because of lack of time. One thing is certain, if we had found that an extended system of two million thermoreceptors has no function in the human body, we would be wrong; we would know that, even before we thought of the problem. Now, what is the significance of these thermoreceptors, Krause's and Ruffini's bodies? They have an overwhelming significance in human temperature control. We do not have only one system of temperature control—the one we have been discussing here—we have two, and the other one I would like to call the Pavlovian system of human temperature control. If we are out on the Argentine beach in the hot sunshine, it will tell us at noontime it is about time to go into the shade of a palm. This is a conditioned reflex; a consciously perceived sensation of temperature, followed by willful action. All these are very powerful mechanisms of a human temperature control which is always active—consciously, subconsciously, half consciously, automatically conditioned, or more or less nonconditioned. Although this mechanism is probably even more powerful than the hypothalamic one, it cannot do one thing: it cannot control our internal temperature precisely. It is just like building a house; one wants to have the thermostat in the living room and not on the front porch. One does not want to have thermostats distributed on the front porch and the rear part of the house; it would just not work out, particularly if we have a cocktail party inside. So this is why we have two mechanisms. The first mechanism provides the wide range of control. It decides whether one wears a fur coat or a Bikini bathing suit and where to go and what sort of shelter to use, whether to air-condition in summer, or how to control the environment in a space vehicle. It is always the same problem. This is Pavlovian control of temperature, using all our means, all the power of human intelligence. But inside, we need the second mechanism to control precisely our internal body temperature. Neither in technology nor in the realm of life has anything ever been controlled unless it was first measured.

Thermogenesis in the acclimated animal[1]

Summary

O. HEROUX
Division of Applied Biology, National Research Council, Ottawa, Canada

COMPARATIVE STUDIES ON SMALL MAMMALS and birds have revealed that the well-known metabolic acclimation observed in white rats exposed to constant cold temperature conditions in the laboratory also exists in some species exposed in nature to the more natural fluctuating climatic conditions. In recent years, a great effort has been made to characterize the metabolic adjustments which provide the small animals with increased cold tolerance after cold acclimation.

It has been clearly shown in the rat that cold acclimation increases nonshivering thermogenesis, and convincing evidence has recently been obtained that noradrenaline is one of the mediators of this nonshivering thermogenesis. During the discussion, the interesting suggestion has been made that noradrenaline might act calorigenically by making more non-esterified fatty acids available to the skeletal muscle.

Although the question of how additional heat is produced in the cold-acclimated animal appears to be partly solved, some doubt remains concerning the site of origin as well as the control of this thermogenesis. Indirect evidence implicates muscle as the tissue responsible for producing heat by means other than shivering in the cold-acclimated rat. Functionally eviscerated cold-acclimated rats have been shown to increase their oxygen consumption on exposure to cold, and also to respond to noradrenaline as well as do the sham-operated cold-acclimated rats. The final answer to this problem, however, will be obtained only when simultaneous measurements of arteriovenous differences in O_2 content and rate of flow of blood through a given muscle are made before and after acclimation to cold.

Concerning the control of thermogenesis, there is still a great deal of uncertainty about the nature of the control in the brain. There would seem to be no question about the existence of cold receptors located in the body-shell tissues which have synaptic (reflex) connections with the hypothalamus thermogenic outflow. Evidence of cold receptors located in the brain has been obtained from isolated pyramidal bundle preparations. This

[1] Contribution from the Division of Applied Biology, National Research Council, Ottawa, Canada; issued as N.R.C. No. 5957.

should be further supported by a demonstration that afferent fibers subserving thermal reflexes do not enter the brain through the unsevered pyramidal bundles or through the intact first, second or third cranial nerves.

It has been well demonstrated that the hypothalamic center is capable of initiating and maintaining vasomotor and sudomotor activities of any observable rate and duration under warm environmental conditions without afferent impulses. It also appears that the anterior hypothalamus is a sensory organ with primary neurons for temperature reception, analogous to those of the retina, but it is not a relay station for afferent impulses from the skin. While this hypothalamic mechanism would be the fine control for regulating our internal temperature precisely, the end organs of Krause and of Ruffini in the skin would be the coarse controls that measure the environmental temperature changes. The role of hypothalamic mechanisms in the regulation of body temperature under conditions of cold needs further clarification.

III

Neurohumoral Response Patterns and Endocrine Functions

Chairmen: ALLEN D. KELLER, E. D. P. DE ROBERTIS AND L. P. DUGAL

Neuroendocrine mechanisms influencing ACTH and TSH secretion and their role in cold acclimation[1]

KARL M. KNIGGE
Department of Anatomy, College of Medicine, University of Cincinnati, Cincinnati, Ohio

IT IS GENERALLY FELT that adaptation to cold environment involves participation of the endocrine system, with a large body of experimental evidence establishing that both adrenal and thyroid glands are stimulated to increased functional activity (1–3). Significant alterations in electrolyte metabolism and in renal and cardiovascular physiology indicate that posterior lobe and electrolyte-regulating hormones are mobilized also in the complex response evoked by cold exposure. The endocrine response to cold involves both an initial acute phase as well as the sustained chronic phase of more prolonged exposure. Accelerated secretion of thyroidal or adrenocortical hormones requires a concomitant increase in the secretion of the respective pituitary tropins, namely thyrotropin (TSH) and corticotropin (ACTH).

The mechanisms of increasing pituitary secretion of TSH and ACTH involve both neural and humoral routes. The former reflect the modulatory influences of the central nervous system upon pituitary gland function; the latter represent the basic positive and negative feed-back interrelationships between the pituitary gland and its respective target organs. The acute endocrine response to cold environment would appear to involve the precipitous activation of the pituitary by neural mechanisms principally. The chronic prolonged endocrine involvement presumably includes both neural and humoral feed-back mechanisms; the relative importance of these two components in chronic cold acclimation is not well understood. Adequate evidence for the role of neural mechanisms in stimulating the endocrine glands during acute cold exposure is seen in the failure of either thyroid or adrenal response when the normal anatomical relationships between pituitary gland and the central nervous system are disturbed.

Severance of the pituitary stalk renders the pituitary-adrenal axis unresponsive to cold exposure (4). Electrolytic destruction of appropriate areas of the hypothalamus (5, 6) or midbrain transection (7) likewise prevent thyroid or adrenocortical response to cold. After removal of the pituitary gland from hypothalamic influence by transplantation to the anterior chamber of the eye, no adrenal (8) or thyroid (9) response is observed after acute cold exposure or after gradual adaptation of the hypophysectomized rat, bearing ocular grafts of the pituitary (K. M. Knigge and W. H. Florsheim, unpublished observations). Some species differences as well as differential sensitivity to acute cold exposure exist, however. Nelson *et al.* (10), measuring adrenal 17-hydroxycorticosteroid secretion rate in the normal dog, found no increased hormone output upon exposure to −10°C; some adrenal activation occurred at −48°C to 78°C (11, 12). Normal human subjects when exposed to 4°C exhibited no evidence of increased adrenal function as reflected by urinary 17-hydroxycorticosteroid excretion (13). No alteration in plasma 17-hydroxycorticosteroids was observed in humans during the course of lowering body temperature preparatory to surgery (14). Under field conditions of chronic cold exposure, soldiers exhibited no significant changes in I^{131} uptake, PBI^{131} or conversion ratio compared to their pre-exposure measurements (15). Ingbar *et al.* (16) found evidence of increased thyroid function in human subjects under more severe laboratory conditions of cold. Acute cold exposure (5–6°C) of several human subjects did not induce any perceptible acceleration in

[1] Supported by National Science Foundation Grant G-9814 and Public Health Service Grant A-3648.

the rate of release of thyroidal I^{131} (D. H. Solomon, personal communication).

ANATOMICAL BASIS FOR NEURAL REGULATION OF PITUITARY FUNCTION

So many outstanding reviews of this subject are available (17–20) that only the briefest statement of this thesis is necessary. The hypothalamus, because of its close anatomical position to the pituitary gland and the presence of an unusual vascular connection between these two, is considered to receive a large variety of neural afferent impulses and to integrate them into a final signal which is transmitted to the pituitary gland where release of specific tropic hormones is stimulated. The nature of the hypothalamic 'signal' is considered to be a chemical transmitter substance, elaborated at or near a primary capillary bed in the median eminence and carried via this portal vascular connection to the sinusoids of the pars distalis. This neurohumoral-pituitary portal system hypothesis is generally accepted; some investigators (21, 22) have outlined a number of objections.

Hypothalamic areas concerned with the regulation of ACTH and TSH respectively will be considered in separate sections below.

Considering the multiplicity of specific and nonspecific sensory stimuli which can influence pituitary activity, it is apparent that the hypothalamic effector sites must receive a complex array of afferent impulses. Elucidation of this intriguing aspect of neuroendocrine control is receiving increasing attention. The several components of the limbic system, in addition to their important role in emotional behavior, have been shown to exert considerable influence on pituitary function. Release of pituitary ovulating hormone can be elicited by electrical stimulation of the amygdaloid nuclei (23, 24). Mason and his co-workers have demonstrated that maximal ACTH release can be achieved by stimulation of the amygdala (25), while bilateral amygdalectomy prevents stress-induced release of ACTH (26); in the rat, destruction of the amygdala results in adrenal atrophy (27). Hippocampal stimulation evokes a rather prolonged period of suppressed ACTH release (25); interestingly, during this period, the threshold for hypothalamic stimulation of ACTH release was increased. Porter (28) observed a similar effect of hippocampal stimulation upon the eosinophenic response to stress. The fornix component of this system has been reinvestigated by Nauta (29), who described fibers from the caudal hippocampal areas terminating in the arcuate (tubero-infundibular) nucleus. The implication of these findings, suggesting a direct hippocampal circuit to a likely terminal site of neurohumoral control, is apparent.

It is becoming clear that the brain stem and the reticular system exert regulating influences on some aspects of hypophysial function. Magoun (30) has somewhat categorically stated that "excitation of the reticular system is the route by which stressful stimuli lead to hypothalamico-pituitary activity and consequent ACTH elaboration." Green (31) has involved the reticular system in proposing a circuitous route by which many modalities of afferent stimulation may play upon the pituitary gland. This path consists of "peripheral afferents → extralemniscal afferent paths in the reticular activating system → lateral hypothalamus → septum → hippocampal formation → amygdala → hypothalamus (by way of the stria and median forebrain bundle)." The findings of Sayers (7) and Anderson *et al.* (32), that midbrain transection prevents stress-induced release of ACTH, constitute significant evidence for the role of the reticular system. Interestingly, the latter workers found that TSH secretion, as measured by rate of release of thyroidal I^{131}, although initially depressed by midbrain sectioning, returned to normal. Smelik (33) proposed alternate afferent pathways for stimulating ACTH release depending upon the nature of the afferent stimuli. He proposed that somatic stimuli ('systemic' stimuli of Fortier (4)) activate pituitary function in the reticular formation pathways, while psychic (neurotropic) stimuli descend from the cortex via the limbic system and fornix to posterior hypothalamus. Abundant corticofugal projections to the reticular formation would appear to provide ample portal for psychic and emotional stresses to affect pituitary function via this route.

Although evidence has been presented (34) that the reticular system is implicated in the control of gonadotropin secretion, Critchlow (35) found that a major part of the brain stem including the reticular formation is nonessential for spontaneous ovulation in the rat. The 'critical structure' suggested by this worker is the mammillary peduncle, arising in the dorsal and deep tegmental nuclei and distributing to mammillary nuclei and median forebrain bundle to the diagonal band. Connections exist from the median forebrain bundle into the pituitary stalk (36). An alternate route from the tegmentum which may be considered is the dorsal longitudinal fasciculus, traversing dorsally over the mammillary region and terminating in the infundibular area.

CORTICOTROPIN

Authoritative reviews covering the several aspects of neural control of ACTH secretion are appearing with consistent regularity (19, 20, 33, 37, 38). There is at present no uniform agreement upon the precise hypothalamic loci concerned specifically with regulation of pituitary ACTH secretion. A majority hold that the integrity of a ventral area extending generally from the median eminence to the mammillary bodies is required for effective neural excitation of ACTH release and increased adrenocortical function; destruction of this neural tissue, without involvement of the portal blood supply to the pituitary, prevents stress-induced release of ACTH but appears to be compatible with a basal rate of ACTH secretion and maintenance of relatively normal

adrenal weight (39–43). Six months after extensive destruction of the median eminence of the rat, Fortier and de Goot (44) found low pituitary ACTH stores, decreased adrenal weight, low plasma corticosteroids and depressed *in vitro* corticosteroidogenesis; this data was interpreted to indicate a marked depression of both release and synthesis of ACTH. Electrical stimulation of various hypothalamic areas results in increased ACTH discharge (25, 28, 45). Employing a technique of direct cannulation and measurement of the rate of corticosterone secretion, Slusher (45a) has reported an apparent dissociation between changes in adrenal ascorbic acid concentration and venous effluent corticosterone secretion; lesions in the posterior and more central hypothalamic region were considered to be concerned specifically with corticosterone secretion. It seems likely that such results may reflect only relative impairment of a single neural mechanism; it is pertinent to note that as an index of ACTH secretion, the measurement of corticosterone secretion is a considerably more sensitive parameter than adrenal ascorbic acid concentration (46). The localization of an ACTH-regulating area in posterior tubero-hypothalamic areas cannot be reconciled with the data of Anand *et al.* (47, 48), Smelik (33) and Koibuchi (49) which localize an ACTH area in anterior hypothalamus and of Hume (50, 51) who believes an anterior median eminence area is involved. Endröczi and Mess (52) found electrolytic destruction of the tuberal nuclei to be effective in preventing release of ACTH; lesions in the posterior hypothalamus had no influence. Because of its close anatomical position to the primary capillary bed of the portal vessels, the arcuate nucleus (n. infundibularis) has been frequently considered as an active ACTH-regulating site (53). Schmid *et al.* (54, 55) consider the ventro- and dorsomedial hypothalamic nuclei to be sites influential in ACTH control. In support of his evidence that vasopressin is the hypothalamic excitor material, McCann (56, 57) contends that destruction of the supraoptico-hypophysial tract is required for effective interference with ACTH release. Story *et al.* (58) found that adrenal cortical secretion in the dog persists in response to stress up to 6 hours after removal of the entire brain including hypothalamus. Additional experiments by this group (59) have led to the suggestion that an ACTH neurohumor arises from an area between low medulla and the inferior collicular level. In these experiments, the entire brain of the dog above the pituitary was removed: transection of the cord at low medulla level abolished adrenocortical response to thermal and operative trauma. These experiments necessarily imply that the suggested neurohumor is delivered to the pituitary gland via the peripheral circulation.

Species differences, operative techniques or parameters of measurement alone cannot account for the divergent results obtained thus far in elucidating hypothalamic influence on ACTH secretion. The difficulty in synthesizing a clear picture of neural control of ACTH may be due in part to the fact that interpretation of data has been based upon the assumption of a single neural excitatory mechanism which serves only to evoke release of ACTH. Sufficient circumstantial evidence appears to be present to suggest the possibility of a dual mechanism, consisting of both excitatory and inhibitory components. The experiments of Mason (25, 26) and Porter (28), indicating a suppressive effect of hippocampal stimulation, have been cited previously. Observing that fornix transection induced alert and active behavior, Green and Arduini (60) suggested an inhibitive influence of hippocampus on the posterior hypothalamus. In rats with certain hypothalamic lesions of the posterior hypothalamus, Bouman *et al.* (61) observed a stress-induced fall in ascorbic acid concentration greater than that seen in normal animals subjected to similar stress. Roberts and Keller (62), studying *in vitro* respiration and aerobic glycolysis of hypothalamic and hypophysial tissue, found that cortisone administration (*in vivo*) resulted in increased metabolism of posterior hypothalamus with a concomitant depression in adenohypophysial respiration and suggested an inhibitory neural pathway in the posterior hypothalamic-hypophysial system. Brodish and Long (63) and Sayers (7) found that following the stresses of bilateral adrenalectomy or ether anesthesia, respectively, peripheral blood concentration of ACTH rose abruptly but then fell to subnormal values before a sustained high level was again achieved. Knigge *et al.* (64) and Henkin and Knigge (65) observed a similar initial biphasic response in the pattern of corticosterone secretion by the rat following scalding, immobilization or high-intensity sound. The period of adrenocortidal suppression was not an exhaustive phenomenon on the part of the adrenal or pituitary and could be prevented by hypothalamic lesions or by pharmacological blockade. Slusher and Critchlow (66) noted that, after surgical stress, some rats with midbrain lesions exhibited rates of corticosterone secretion which were greater than found in nonlesioned animals.

The identity of the hypothalamic corticotropin releasing factor(s) is receiving intensive study by many investigators. The presence of a portal excitor material is demonstrated by the observations of Porter *et al.* (67–70) that a substance in lyophilized plasma collected from the pituitary portal vessels of the hypophysectomized dog is effective in producing ascorbic acid depletion using the hydrocortisone-blocked rats as assay animals. Additional work of McCann (56, 57) and that of others (71–73) continues to place vasopressin (some material evolved in the supraoptico-hypophysial tract) in the forefront of the possible ACTH-stimulating chemotransmitters. Nowell (74) has suggested that neurohypophysial hormones are involved in release of ACTH in response to systemic stresses but not to emotional ones. Recent findings by Royce and Sayers (75) and Hilton *et al.* (76) have shown that vasopressin may have a potentiating effect on circulating ACTH as well as a direct action on stimulating cortical secretion. Sayers (7) and Royce and Sayers (77) have reported that an

acid extract of ventral hypothalamus, but not Pitressin, is effective in releasing ACTH in their assay animal (adrenalectomized rat with brain-stem transection at upper pons). In these experiments, it is not clear how brain-stem transections interfere with the action of Pitressin in releasing or potentiating peripheral stores of ACTH. In dogs with transection of the pituitary stalk, Koibuchi and Fukuda (78) found increased blood concentration of ACTH and 17-hydroxycorticosteroids; the stresses of laparotomy and burning were able to elicit increased pituitary-adrenal and gonadal function in the stalk-sectioned dog and the authors concluded that the humoral transmitter must be transmitted to the hypophysis via the systemic circulation.

Saffran and Schally (79, 80) and Guillemin *et al.* (81) have reported the isolation of a peptide CRF or hypophysiotropic factor different from vasopressin. Crude CRF material is chromatographically different from oxytocin, vasopressin and ACTH (82). In various stages of purification, the CRF material is reported to be more potent in its ACTH releasing ability than an equal weight of lysine vasopressin. The specificity of the initial *in vivo* tests used, however, based upon the release of corticotropin from the rat pituitary gland during incubation, has been seriously questioned (83–85). To overcome these objections, Guillemin *et al.* (46) have used *in vitro* tests (hypothalamic-lesioned rats and rats blocked with Nembutal-morphine) to show that a CRF preparation (fraction D) possesses greater ACTH releasing effect than equivalent pressor units of lysine vasopressin.

THYROTROPIN

Electrolytic destruction of various hypothalamic regions results in a disability on the part of the pituitary gland in supplying increased amounts of thyrotropin under a variety of experimental conditions (cold exposure, goitrogens, subtotal thyroidectomy) which normally evoke thyroid responses (86–89). As in the case of ACTH, attempts to find hypothalamic areas concerned with TSH secretion have likewise not yielded specific localizations. Although it is generally felt that anterior hypothalamus is the region most involved, the amount of hypothalamic destruction necessary to produce TSH deficiency is relatively enormous, frequently incompatible with life of the animal, and suggests that the TSH-regulating mechanisms in the hypothalamus may be considerably more diffuse than those which exist for ACTH. The pituitary disability resulting from hypothalamic destruction in the rat appears to be an inability to synthesize and release sufficient TSH to maintain normal serum levels (90–92). Of considerable significance was the finding of D'Angelo (93) that the depletion of pituitary TSH stores attendant upon goitrogen feeding and the 'rebound' to supranormal levels upon withdrawal were not materially influenced by hypothalamic lesions. This investigator has summarized the opinion of several workers that the pituitary appears to have a relatively greater degree of autonomous function with respect to

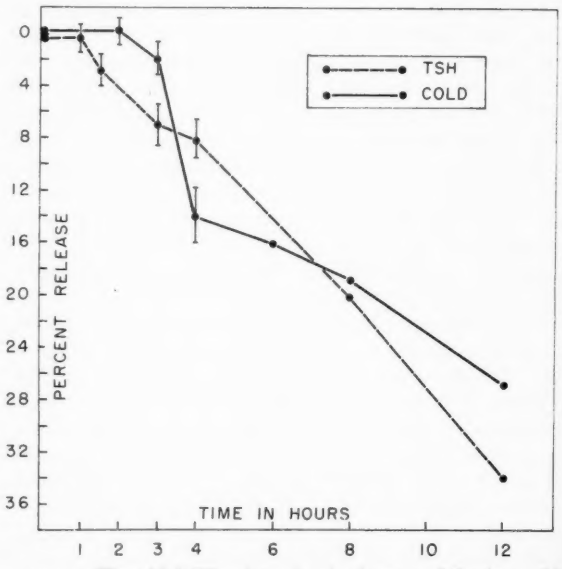


FIG. 1. Thyroidal I^{131} release in the hamster following cold exposure or thyrotropin administration.

TSH secretion. Woods and Bard (94) observed a normal uptake and rate of thyroidal I^{131} release in the 'isolated hypothalamus' cat preparation.

Although there may be a substantial degree of pituitary-thyroid function independent of neural influence, the nervous system can exert effects upon acute and chronic thyroid activity. Electrical stimulation of hypothalamus evokes accelerated thyroidal I^{131} release in the rabbit (95–96) and cat (97); Greer (98) was unable to produce accelerated release in the rat by radio-stimulation of the hypothalamus. An influence of epithalamus is suggested by the experiments of Mess (99, 100) in which electrolytic destruction of the habenula nuclei interfered with TSH secretion as reflected by a failure of the fall in pituitary TSH content following thyroidectomy or thyroid hypertrophy in response to iodine deficient diet or propylthiouracil. The depressing effect of exogenous thyroxine upon thyroid weight and histology and pituitary TSH content was notably modified by lesions in the habenular nuclei (101). Intentional or coincidental activation of ACTH discharge and adrenocortical secretion generally results in temporary inhibition of TSH release (102–104). The interplay of neural mechanisms for control of these two hormones in chronic cold exposure is not clear. Acute cold exposure of the rat (105), rabbit (106) or hamster (5) activates a neural mechanism for rapid discharge of TSH. Increased blood TSH is detectable within 30 minutes of cold exposure of the rabbit; maximal amounts (500-fold increase) are achieved after 3 hours (107). In the hamster, accelerated release of thyroidal I^{131} occurs at 5°–6°C without any apparent adrenocortical intervention (108). Within 12 hours of cold exposure, thyroidal hormone stores are depleted by more than 45% (109). Figure 1 compares the

time sequence of accelerated release from the hamster thyroid attendant upon acute cold exposure with that produced by exogenously administered TSH. No accelerated release occurs during the first 2 hours of cold. At 3 hours a detectable (but not statistically significant) change in the rate of release is seen, while a maximal rate is achieved during the 3rd to 4th hour of cold. A significant acceleration in thyroidal I^{131} release produced by exogenous TSH (1 unit) is first observed 1.5 hours after administration. This accelerated rate continues at approximately the same slope throughout the 12-hour period studied and produces a slightly greater final per cent release than does 12 hours of cold exposure. During the critical period of the first 4 hours of cold exposure, PBI levels do not change significantly. TSH concentration in the normal hamster pituitary is 0.68 ± 0.11 mU/mg. After 0.5 hours of cold, some indication of TSH release was seen; a 60 per cent decrease in TSH concentration was found after 1 hour and this decreased further until a concentration of 0.16 mU/mg was present 7–12 hours after cold. The amount of TSH depleted from the gland during the 1st hour of cold exposure represents approximately 80% of the total released during an entire 12-hour period.

Identification of the hypothalamic material active in releasing TSH has not been investigated extensively. Dubreuil and Martini (110), Martini *et al.* (111), Bottari (107) and Bottari and Martini (112) have implicated the neurohypophysial hormones as possible TSH releasing factors. Although thyroxine administration decreases markedly the concentration of neurosecretory material in the paraventricular nucleus, posterior pituitary extracts have no effect on thyroid I^{131} uptake or rate of release (113, 114). The concentration of thyroxine and tri-iodothyronine in the posterior lobe of the pituitary (113, 115) has been appealing evidence to link neurohypophysial hormones with regulation of TSH secretion. This possibility is weakened seriously by the observation that a similar concentration of thyroxine and tri-iodothyronine occurs in the atrophic, nonfunctional posterior lobe of the rabbit following stalk sectioning (116). This concentrating effect does not appear to be restricted to thyroxine only since cortisone-C^{14} was found to localize here also (117). Furthermore, many species including rat, guinea pig and cat, do not exhibit greater thyroxine concentration in the posterior lobe (118, 119). Shibusawa *et al.* (120) have reported that an aqueous extract of dog anterior hypothalamus was effective in increasing plasma concentration of TSH and PBI; daily injection of this hypothalamic material prevented the decline in I^{131} uptake which normally follows stalk sectioning in the dog (121). This group of workers also reported recently the effectiveness of their thyrotropin releasing factor (TRF) in promoting increased thyroid weight and T/S ratio in the lesioned rat (122).

The question of the site of action of thyroxine in the feed-back control of TSH secretion is of principal importance. A direct action of thyroxine at the pituitary level is indicated by: *a*) a depression of TSH secretion from pituitary ocular grafts following thyroxine administration (9, 123); *b*) inhibition of TSH secretion following microinjection of thyroxine directly into the pituitary (124, 125); *c*) depression of TSH secretion after thyroxine injection in spite of the presence of large hypothalamic lesions (90, 91); lesions which produced diabetes insipidus were also ineffective in altering the depressing effect of thyroxine depressing TSH secretion at the pituitary level; it does not necessarily follow that lowered thyroxine levels stimulate TSH synthesis or release at the pituitary. Both positive and negative feedback effects at the pituitary level are implied in the thesis of Brown-Grant (126) that the portal blood concentration of thyroxine is adjusted in the hypothalamus and that the resulting increased or decreased thyroxine levels reaching the pituitary effect a corresponding depression or elevation in TSH output. In contrast, Söderberg (127) has proposed that the pituitary responds not to blood levels of thyroxine but rather to the amount of thyroxine accumulated in the pituitary, with rates of intracellular accumulation and breakdown determining the rate of TSH secretion.

REFERENCES

1. Sayers, G. *Physiol. Rev.* 30: 241, 1950.
2. Stevens, C. E., S. A. D'Angelo, K. E. Paschkis, A. Cantarow and F. W. Suderman. *Endocrinology* 56: 143, 1955.
3. Sellers, E. A. *Rev. can. biol.* 16: 175, 1957.
4. Fortier, C., G. W. Harris and I. R. McDonald. *J. Physiol.* 136: 344, 1957.
5. Knigge, K. M. and S. M. Bierman. *Am. J. Physiol.* 112: 625, 1958.
6. Brolin, S. E. *Acta anat.* 2, Suppl. 3, 1945.
7. Sayers, G. *Ciba Foundation Colloquia on Endocrinology* 11: 138, 1957.
8. Fortier, C. and H. Selye. *Am. J. Physiol.* 159: 433, 1949.
9. Von Euler, C. and B. Homgren. *J. Physiol.* 131: 137, 1956.
10. Nelson, D. H., R. H. Egdahl and D. M. Hume. *Endocrinology* 58: 184, 1955.
11. Hume, D. M., R. H. Egdahl and D. H. Nelson. *The Physiology of Induced Hypothermia.* Washington: Nat. Acad. Sc., 1955, p. 170.
12. Egdahl, R. H. and J. B. Richards. *Am. J. Physiol.* 185: 239, 1956.
13. Thorn, G. W. and J. C. Laidlow. *Tr. Am. Clin. & Climatol. A.* 179: 199, 1953.
14. Bernhard, W. F. *The Physiology of Induced Hypothermia.* Washington: Nat. Acad. Sc., 1955, p. 175.
15. Rodahl, K. and G. Bang. Arctic Aeromedical Laboratory Report 57–36, 1957.
16. Ingbar, S. H., C. R. Kleeman, M. Quinn and D. E. Bass. *Clin. Res. Proc.* 2: 86, 1954.
17. Harris, G. W. *Neural Control of the Pituitary Gland.* London: Arnold, 1955.
18. Benoit, J. and I. Assenmacher. *J. physiol, Paris,* 47: 427, 1955.
19. Donovan, B. T. and G. W. Harris. *Ann. Rev. Physiol.* 19: 439, 1957.
20. Fortier, C. and J. de Groot. *Prog. Neurol. and Psychiat.* 13: 118, 1958.

21. THOMPSON, A. P. D. AND S. ZUCKERMAN, *Nature, London* 175: 74, 1955.
22. GAUPP, V. AND H. SPATZ. *Acta neuroveg.* 12: 285, 1955.
23. SHEALY, C. N. AND T. L. PEELE. *J. Neurophysiol.* 20: 725, 1957.
24. BUNN, J. P. AND J. S. EVERETT. *Proc. Soc. Exper. Biol. & Med.* 96: 369, 1957.
25. MASON, J. W. *Reticular Formation of the Brain.* Boston: Little, 1957, p. 646.
26. MASON, J. W., W. J. H. NAUTA, J. V. BRADY AND J. A. ROBINSON, *Proc. Endocr. Soc.* 1959, p. 29.
27. WOODS, J. W. Ph.D. Thesis, Johns Hopkins Univ., 1954.
28. PORTER, R. W. *Recent Progr. Hormone Research.* 10: 1, 1954.
29. NAUTA, W. H. J. *J. Comp. Neurol.* 104: 247, 1956.
30. MAGOUN, H. W. *The Waking Brain.* Springfield: Thomas, 1958.
31. GREEN, J. D. *Hypothalamic-Hypophysial Interrelationships,* edited by W. S. Fields, R. Guillemin and C. A. Carton. Springfield: Thomas, 1956, p. 3.
32. ANDERSON, E., R. W. BATES, E. HAWTHORNE, W. HAYMAKER, K. KNOWLTON, D. MCK. RIOCH, W. T. SPENCE AND H. WILSON. *Recent Progr. Hormone Research.* 13: 21, 1957.
33. SMELIK, P. S. *Autonomic Nervous Involvement in Stress-Induced ACTH Secretion.* Assen: H. Born, 1959.
34. SAWYER, C. H. *Reticular Formation of the Brain.* Boston: Little, 1957, p. 223.
35. CRITCHLOW, V. *Endocrinology.* 63: 596, 1958.
36. GREEN, J. D. *Am. J. Anat.* 88: 225, 1951.
37. FORTIER, C. XX Internat. Physiological Congress, Brussels, 1956.
38. GUILLEMIN, R. *Hypothalamic-Hypophysial Interrelationships.* Springfield: Thomas, 1956, p. 46.
39. GANONG, W. F. AND D. M. HUME. *Endocrinology.* 55: 474, 1954.
40. LAQUER, G. L., S. M. MCCANN, L. H. SCHREINER, E. ROSENBERG, E. ANDERSON AND D. M. MCK. RIOCH, XIX Internat. Physiological Congress, 1953, p. 542.
41. MCCANN, S. M. *Am. J. Physiol.* 175: 13, 1953.
42. GREER, M. A. AND H. ERWIN. *Endocrinology.* 58: 665, 1956.
43. BOGDANOVE, E. M. *Endocrinology.* 60: 689, 1957.
44. FORTIER, C. AND J. DE GROOT. XXI Internat. Physiological Congress, Buenos Aires, 1959.
45. DE GROOT, J. AND G. W. HARRIS. *J. Physiol.* 111: 335, 1950.
45a. SLUSHER, M. A. *Endocrinology* 63: 412, 1958.
46. GUILLEMIN, R., W. E. DEAR, B. NICHOLS AND H. S. LIPSCOMB. *Proc. Soc. Exper. Biol. & Med.* 101: 107, 1959.
47. ANAND, B. K. AND S. DUA. *J. Physiol.* 127: 153, 1955.
48. ANAND, B. K. P. RAGHUNATH, S. DUA AND S. MOHINDRA. *Indian J. M. Res.* 42: 231, 1954.
49. KOIBUCHI, E. *Endocrinol. Japon.* 5: 89, 1958.
50. HUME, D. M. *Reticular Formation of the Brain.* Boston: Little, 1957, p. 231.
51. HUME, D. M. AND B. T. JACKSON. *Proc. Endocr. Soc.* 1959, p. 31.
52. ENDRÖCZI, E. AND B. MESS. *Endokrinologie.* 33: 1, 1955.
53. COTTLIER, E. XXI Internat. Physiological Congress, Buenos Aires, 1959.
54. SCHMID, R., L. GONZALO, R. BLOBEL, E. MUSCHKE AND E. TONUTTI. *Endokrinologie* 34: 65, 1957.
55. SCHMID, R., L. GONZALO, R. BLOBEL, E. MUSCHKE AND E. TONUTTI. *Folia endocrinol.* 10: 3, 1957.
56. MCCANN, S. M. *Endocrinology* 60: 664, 1957.
57. MCCANN, S. M. AND A. FRUIT. *Proc. Soc. Exper. Biol. & Med.* 96: 566, 1957.
58. STORY, J. L., J. C. MELBY, R. H. EGDAHL AND L. A. FRENCH. *Am. J. Physiol.* 196: 583, 1959.
59. EGDAHL, R. H. *Proc. Endocr. Soc.* 1959, p. 30.
60. GREEN, J. D. AND A. A. ARDUINI. *J. Neurophysiol.* 17: 533, 1954.
61. BOUMAN, P. R., J. H. GAARENSTROOM, P. G. SMELIK AND D. DEWIED, *Acta physiol. et pharmacol. Neerl.* 6: 368, 1957.
62. ROBERTS, S. AND M. A. KELLER. *Endocrinology* 57: 64, 1955.
63. BRODISH, A. AND C. N. H. LONG. *Endocrinology* 59: 666, 1956.
64. KNIGGE, K. M., C. H. PENROD AND W. H. SCHINDLER, *Am. J. Physiol.* 196: 579, 1959.
65. HENKIN, R. I. AND K. M. KNIGGE. *Proc. Soc. Exper. Biol. & Med.* In press.
66. SLUSHER, M. A. AND J. CRITCHLOW. *Fed. Proc.* 18: 145, 1959.
67. PORTER, J. C. AND J. C. JONES. *Endocrinology* 58: 62, 1956.
68. PORTER, J. C. AND H. W. RUMSFELD. *Endocrinology* 58: 359, 1956.
69. RUMSFELD, H. W. AND J. C. PORTER, *Endocrinology* 64: 942, 1959.
70. PORTER, J. C. AND H. W. RUMSFELD. *Endocrinology* 64: 948, 1959.
71. SHIBUSAWA, K., S. SAITO, M. FUKUDA, T. KAWAI, H. YAMADA AND K. TOMIZAWA, *Endocrinol. Japon.* 2: 182, 1955.
72. CASENTINI, S., A. DEPOLI, S. HUKOVIC AND L. MARTINI. *Endocrinology* 64: 483, 1959.
73. SIDEMAN, M. AND H. SOBEL. *Proc. Endocr. Soc.* 1959, p. 32.
74. NOWELL, N. W. *Endocrinology* 64: 191, 1959.
75. ROYCE, P. C. AND G. SAYERS. *Proc. Soc. Exper. Biol. & Med.* 98: 70, 1958.
76. HILTON, J. C., L. F. SCIAN, C. D. WESTERMAN AND O. R. KRUESI. *Proc. Soc. Exper. Biol. & Med.* 100: 523, 1959.
77. ROYCE, P. C. AND G. SAYERS. *Fed. Proc.* 18: 132, 1959.
78. KOIBUCHI, E. AND M. FUKUDA. *Endocrinol. Japon.* 5: 11, 1958.
79. SAFFRAN, M. AND A. V. SCHALLY. *Canad. J. Biochem. Physiol.* 33: 408, 1955.
80. SAFFRAN, M., A. V. SCHALLY AND B. G. BENFRY. *Endocrinology* 57: 439, 1955.
81. GUILLEMIN, R., W. R. HEARN, W. R. CHEEK AND D. H. HOUSEHOLDER. *Endocrinology* 60: 488, 1957.
82. SCHALLY, A. V. AND R. GUILLEMIN. *Proc. Endocr. Soc.* 1959, p. 31.
83. ROBERTS, S. *Ciba Foundation Colloquia on Endocrinology* 11: 167, 1957.
84. FORTIER, C. *Texas Rep. Biol. & Med.* 16: 68, 1958.
85. FORTIER, C. AND D. N. WARD. *Canad. J. Biochem. Physiol.* 36: 111, 1958.
86. BOGDANOVE, E. M. *Endocrinology* 60: 689, 1957.
87. GANONG, W. F., D. S. FREDERICKSON AND D. M. HUME. *Endocrinology* 57: 355, 1955.
88. FLORSHEIM, W. H. *Endocrinology* 62: 783, 1958.
89. REICHLIN, S. *Endocrinology* 60: 567, 1957.
90. D'ANGELO, S. A. *J. Endocrinol.* 17: 286, 1958.
91. FLORSHEIM, W. H. *Proc. Soc. Exper. Biol. & Med.* 100: 73, 1959.
92. BOGDANOVE, E. M. AND S. A. D'ANGELO. *Endocrinology* 64: 53, 1959.
93. D'ANGELO, S. A. *Proc. Endocrin. Society,* p. 50, 1959.
94. WOODS, J. W. AND P. BARD. *Fed. Proc.* 18: 173, 1959.
95. HARRIS, G. W. AND J. WOODS. *Nature, London* 178: 80, 1956.
96. CAMBELL, H. J., R. GEORGE AND G. W. HARRIS. *J. Physiol.* 148: 5P, 1959.
97. KNIGGE, K. M. Unpublished observations.
98. GREER, M. A. *Recent Progr. Hormone Research* 13: 67, 1957.
99. MESS, B. *Endokrinologie* 35: 196, 1958.
100. MESS, B. *Endokrinologie* 35: 296, 1958.
101. MESS, B. *Endokrinologie* 37: 104, 1959.
102. BROWN-GRANT, K., G. W. HARRIS AND S. REICHLIN. *J. Physiol.* 126: 41, 1954.
103. BROWN-GRANT, K., G. W. HARRIS AND S. REICHLIN. *J. Physiol.* 126: 29, 1954.
104. HARRIS, G. W. *Ciba Foundation Colloquia on Endocrinology.* 8: 531, 1955.
105. BROWN-GRANT, K. *J. Physiol.* 131: 52, 1956.
106. BROWN-GRANT, K., C. VON EULER, G. W. HARRIS AND S. REICHLIN. *J. Physiol.* 126: 1, 1954.
107. BOTTARI, P. *Ciba Foundation Colloquia on Endocrinology.* 11: 52, 1957.
108. KNIGGE, K. M., R. S. GOODMAN AND D. H. SOLOMON. *Am. J. Physiol.* 189: 415, 1957.
109. KNIGGE, K. M. XXI Internat. Physiological Congress, Buenos Aires, 1959.

110. DUBREUIL, R. AND L. MARTINI. XX Internat. Physiological Congress, Brussels, 1956.
111. MARTINI, L., A. DE POLI AND S. CURI. *Proc. Soc. Exper. Biol. & Med.* 91: 490, 1956.
112. BOTTARI, P. AND L. MARTINI. *Intern. J. Appl. Radiation and Isotopes* 3: 81, 1958.
113. CURRIER, R. *Ciba Foundation Colloquia on Endocrinology* 10: 21, 1957.
114. REICHLIN, S. *Endocrinology* 60: 470, 1957.
115. FORD, D. H., M. POSNER AND J. GROSS. *Anat. Record* 121: 294, 1954.
116. TAUROG, A., G. W. HARRIS, W. TONG AND I. L. CHAIKOFF. *Endocrinology* 59: 34, 1956.
117. CURRIER, R. AND L. ZIZINI. *Compt. rend.* 242: 315, 1956.
118. FORD, D. H. AND J. GROSS. *Endocrinology* 62: 416, 1958.
119. FORD, D. H., S. KANTOUNIS AND R. LAWRENCE. *Endocrinology* 64: 977, 1959.
120. SHIBUSAWA, K., S. SAITO, K. NISHI, T. YAMAMO TO K. TOMIZAWA, AND C. ABE. *Endocrinol. Jap.* 3: 116, 1956.
121. SHIBUSAWA, K., S. SAITO, K. NISHI, T. YAMAMOTO, C. ABE, AND T. KAWAL. *Endocrinol. Japon.* 3: 151, 1956.
122. SHIBUSAWA, K., K. NISHI AND C. ABE. *Endocrinol. Japon.* 6: 31, 1959.
123. SCOW, R. O. AND M. A. GREER. *Endocrinology* 56: 590, 1955.
124. VON EULER, C. AND B. HOLMGREN. *J. Physiol.* 131: 125, 1956.
125. YAMADA, T. AND M. A. GREER. *Endocrinology* 64: 559, 1959.
126. BROWN-GRANT, K. *Ciba Foundation Colloquia on Endocrinology* 10: 97, 1957.
127. SÖDERBERG, U. *Acta physiol. scandinav.* 42, Suppl. 147, 1958.

Adenohypophysial function in the guinea pig at low environmental temperature[1]

S. A. D'ANGELO
Daniel Baugh Institute of Anatomy, Jefferson Medical College, Philadelphia, Pennsylvania

D'ANGELO, S. A. *Adenohypophysial function in the guinea pig at low environmental temperature.* Fed. Proc. 19, Suppl. No. 5: 51–56. 1960.—The functional status of the pituitary-thyroid and adrenal systems was assessed in guinea pigs and rats maintained at moderately low temperatures (4–9°C.) for 1–10 weeks by measurement of BMR, serum protein-bound iodine, thyroidal I^{131} release rate, TSH content of blood and hypophysis, S^{35}-methionine tissue uptake, corticoid excretion, adrenal ascorbic acid, and pituitary ACTH, and by evaluation of gland morphology. The relationship of target gland functions to neural mechanisms was studied in cold-exposed animals after electrocautery of the hypothalamus. The results underscore the crucial role of the adenohypophysis in cold acclimation of the rodent.

FEW EXPERIMENTAL PROCEDURES induce as profound a change in anterior pituitary function of the homeothermal animal as does exposure to cold. The secretory alterations in the adenohypophysis reflect the strategic role of this gland in neuroendocrine integration. Through a unique anatomic and physiologic relationship with the hypothalamus and by virtue of its trophic hormone regulation of target gland function, the anterior hypophysis insures effective hormonal contribution to the cold acclimation process. The mechanisms basic to endocrine readjustment at low temperatures are by no means understood; some await precise identification. (This aspect of the subject is treated more fully in another symposium article, by Knigge.) Although the specific hypothalamic-hypophysial interactions have not been elucidated, there is convincing evidence that in acute exposure to cold hypothalamic stimuli quickly facilitate significant shifts in trophic hormone secretion by the pituitary. The nature, magnitude, duration and temporal sequence of these hormone responses to a cold stimulus, and their relationship with the hypothalamus are major facets of the problem which need clarification. This report is primarily concerned with an analysis of some of these endocrine factors in guinea pigs chronically exposed to moderately low temperatures (4–9°C). Comparative observations on the rat are also considered.

[1]Supported by Grant A-432, National Institutes of Health.

PITUITARY-THYROID SYSTEM

The relative importance of thyroidal versus extrathyroidal factors in thermogenesis has not been assessed in most species but most investigators agree that successful thermoregulation in the cold-exposed rodent is often associated with histologic activation of the thyroid gland. Single parameters of thyroid function rarely disclose an accurate picture of pituitary-thyroid interaction in chronic cold exposure, however. This is illustrated by the data of Stevens, D'Angelo and associates (1) on guinea pigs maintained at 6° ± 2°C for periods of 1–10 weeks (fig. 1). Although increased oxygen consumption and histologic activation of the thyroid were noted, 24-hour I^{131} uptake by the gland and serum protein-bound iodine levels were not appreciably altered. This elevation of the

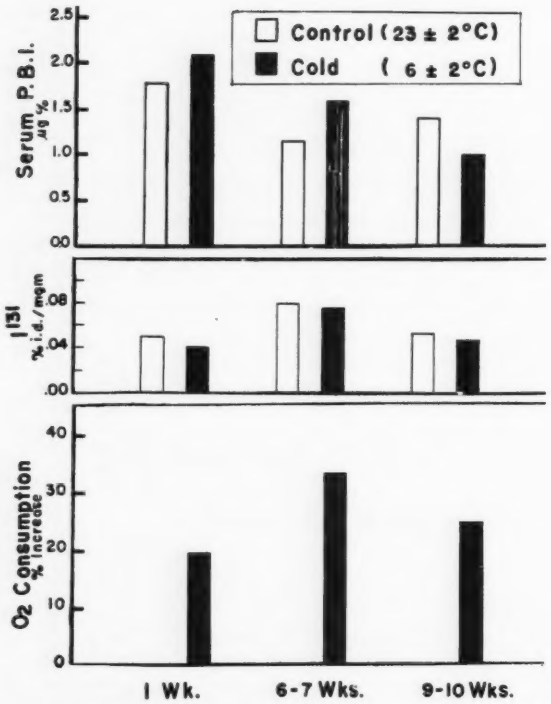


FIG. 1. Serum protein-bound iodine, thyroid I^{131} uptake, and BMR of guinea pigs exposed to cold. Heights of *open* and *solid bars* represent mean values for groups of normal and cold-exposed guinea pigs respectively. Differences in serum PBI and 24-hr. I^{131} uptake by the thyroid (expressed as % of the injected dose per mg of wet tissue) are not statistically significant. BMR is indicated as mean % increase in O_2 consumption from normal level (room temperature).

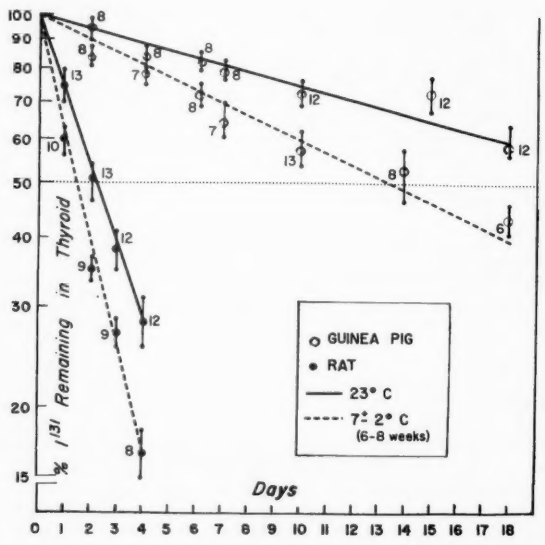


FIG. 2. Thyroidal I^{131} release rates in guineand pigs a rats exposed to cold. Curves drawn through *open* and *solid circles* show thyroidal I^{131} release rates for the guinea pig and rat respectively, at normal (*solid line*) and low (*broken line*) temperatures. Number opposite each point indicates the number of determinations made (1 per animal). *Vertical lines* signify standard error of the mean. Zero time (24–48 hr. after intraperitoneal injection of the tracer dose) represents the time of 100% accumulation of radioiodine in the thyroid. Re-entry of I^{131} into the rat thyroid was blocked with propylthiouracil.

BMR in the presence of normal or even lowered serum PBI levels has also been found in the refrigerated rat (2–4) and in this species thyroidal radioiodine uptake in the cold may be highly variable. A comparison of I^{131} release rate by the thyroid in rat and guinea pig reveals that the tempo of thyroid hormone secretion after 6–8 weeks of cold exposure is significantly increased in both species (fig. 2). The relatively slow release rate in the guinea pig at normal room temperatures (estimated biological half life of 26 days) was approximately doubled in the cold. In the female rat the normally rapid I^{131} release from the thyroid increased from a rate of 25% to about 40% per day, an increase comparable to that shown by the male rat (5). Other basic differences in the pituitary-thyroid system of these rodents have been documented elsewhere (6). The failure of I^{131} uptake methods to indicate enhanced thyroid secretion in the cold-exposed animal in all probability reflects fluctuations in dietary levels of circulating iodine, in renal and fecal excretion, and in the body iodide space. These factors do not modify appreciably the release rate of labeled hormone from the thyroid. The presence of essentially normal circulating levels of thyroid hormone, as measured by serum protein-bound iodine is more pertinent to the "modus operandi" of pituitary-thyroid interplay in the refrigerated animal. These results and those of others (5, 7) strongly suggest that the increased secretion of thyroid hormone necessary for thermogenesis during chronic exposure to cold is balanced by a commensurate utilization and disposal of the hormone at the tissues. Under these circumstances, it is conceivable that even temporary excesses in circulating thyroid hormone could suppress pituitary TSH function through the feed-back mechanism and thus deprive the cold-exposed animal of its proper balance of target hormone. Relatively low blood levels of thyroid hormone thus permit continued secretion of TSH from the pituitary. The results of bio-assay experiments on TSH in both serum and adenohypophysis (fig. 3) support this thesis. Serum TSH titers were appreciably elevated as early as the 1st week of exposure to cold and remained so throughout a 10-week period. Adenohypophysial TSH stores, though within normal limits at the end of the first week, subsequently increased to achieve values 300%–700% of normal. This augmentation of TSH secretion to prolonged cold was accompanied by profound cytological and histochemical changes in the adenohypophysial basophils (fig. 4), lending further support to already convincing evidence which indicates that, in the rodent, genesis of TSH resides in the pituitary basophils (8, 9). Pituitary acidophils were cytologically active and it is noteworthy that the growth of the guinea pig continues unaffected at these moderately low temperatures.

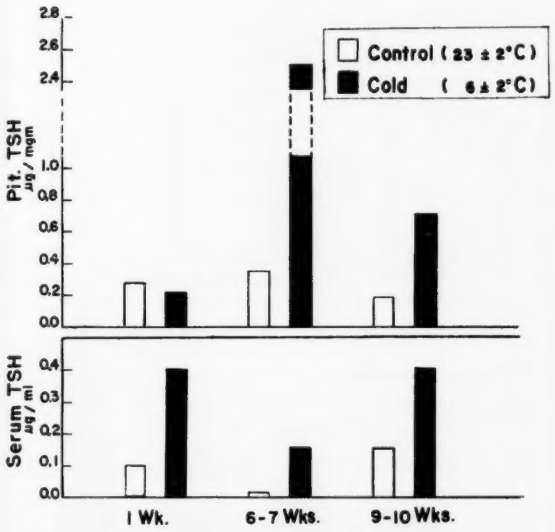


FIG. 3. TSH concentrations in anterior pituitary and in sera of guinea pigs exposed to cold are given in terms of a commercial preparation for which 1 µg was approx. equal to 2 mU of the U.S.P. Reference Standard. Bio-assay of TSH was done by the stasis tadpole method (26). Values show mean concentrations based on injection of 1 mg equivalent of an acid saline extract of pooled adenohypophyses and 0.25 ml. of untreated serum.

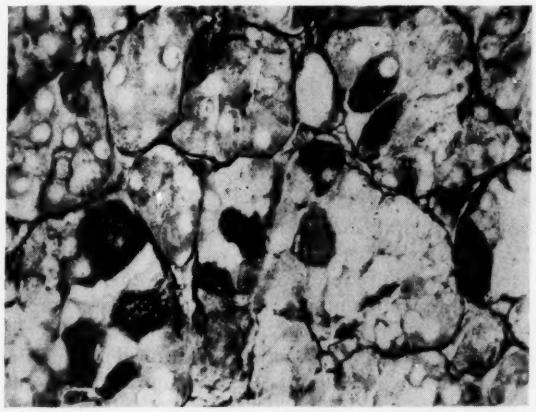


FIG. 4. The histochemical response of the pituitary basophils to cold is shown in a portion of the pars distalis of a guinea pig after 10-wk. exposure. The basophils are enlarged (polygonal dark cells with unstained nuclei) and display abundant glycoprotein granulation selectively stained with aldehyde fuchsin. Basement membranes are also well stained but acidophils and chromophobes are aldehyde fuchsin negative. Helly; Gomori's Aldehyde Fuchsin. ×420.

The sustained augmentation of TSH secretion (and ACTH secretion, *vide infra*) elicited by cold would be expected to involve significant changes in the biochemistry of the adenohypophysis. Metabolic and enzymatic studies of the gland are scanty, however, and any biochemical events unique to synthesis, storage or release of the anterior pituitary hormones have not yet been uncovered. In a probing study on the rat, Levey and Roberts (10) found that after surgical or chemical thyroidectomy—procedures which augment TSH secretion—*in vitro* oxygen consumption of the pituitary rose, whereas lactate production, glucose utilization and levels of cytochrome oxidase and succinic dehydrogenase were unchanged. Accentuated elaboration of other trophic hormones following either adrenalectomy or castration was not accompanied by significant change in respiration or in enzymatic levels. Results of the few radiometric studies available are also inconclusive. Radiophosphorus uptake by the rat pituitary was increased after unilateral adrenalectomy; P^{32} accumulation in the remaining hypertrophied adrenal was decreased (11). The *in vitro* incorporation of S^{35}–labeled methionine into pituitary protein of albino rats was much higher in the anterior than in the posterior pituitary and greater during the first 2 weeks of life, but differences in gonadotrophic hormone secretion (estrous cycle and pregnancy) were apparently not reflected in the ability of pituitary tissue to incorporate methionine into its protein (12).

The results of a comparative *in vivo* study on S^{35}–labeled methionine uptake by thyroid, adenohypophysis and liver tissues of rats and guinea pigs exposed to 5 °C for 6–7 weeks are graphed in figure 5. A marked difference was found in both species with respect to thyroidal uptake which was substantially increased in the rat but not in the guinea pig. Methionine accumulation in the adenohypophysis decreased with cold, significantly so in the case of the rat. Calculation of tissue-blood radioactivity ratios however, tended to minimize any differences which existed between normal and refrigerated animals. The increased accumulation of labeled methionine in the rat thyroid is unexplained. It is evident that heightened pituitary TSH and thyroid hormone secretion in both species do not correlate well with labeled methionine uptake of their respective tissues.

PITUITARY-ADRENAL SYSTEM

The response of the guinea pig's pituitary-adrenal system to cold is no less vigorous than that of the pituitary-thyroid axis. Adult female guinea pigs maintained at 7° ± 2°C for 7 weeks showed significant increases in adrenal-body weight ratios and in urinary excretion of corticoids while ascorbic acid concentrations within the adrenal remained normal (fig. 6). Enhanced adrenal function was clearly referable to augmented ACTH secretion by the adenohypophysis. It was demonstrated in two separate bio-assay experiments that ACTH concentration in the pituitary of the refrigerated guinea pig was increased 10–15 fold (fig. 7). A rise in the level of corticoid excretion, noted within the 1st week of exposure, reached a peak value at the end of the 5th week.

The effects of high level dosage of ascorbic acid and hydrocortisone on pituitary-adrenal function in the guinea pig are shown in figure 6. Intraperitoneal injections of sodium ascorbate (100 mg daily for 46 days) did not prevent the rise in corticoid excretion and the

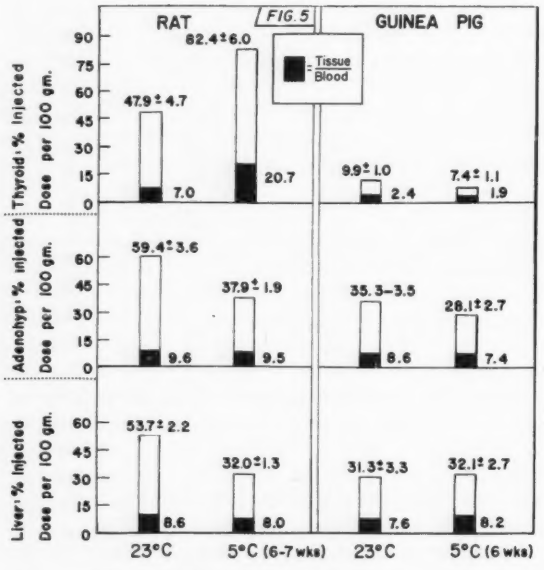


FIG. 5. S^{35}-methionine uptake of the wet tissues in rat and guinea pig at low environmental temperatures was measured 24 hr. after intraperitoneal injection of the tracer dose (25μc). Values above *open bars* indicate mean % uptake ±S.E.M. of the injected dose per 100 g tissue. The value adjacent to *solid portion* of the bar expresses the ratio of tissues to serum radioactivity.

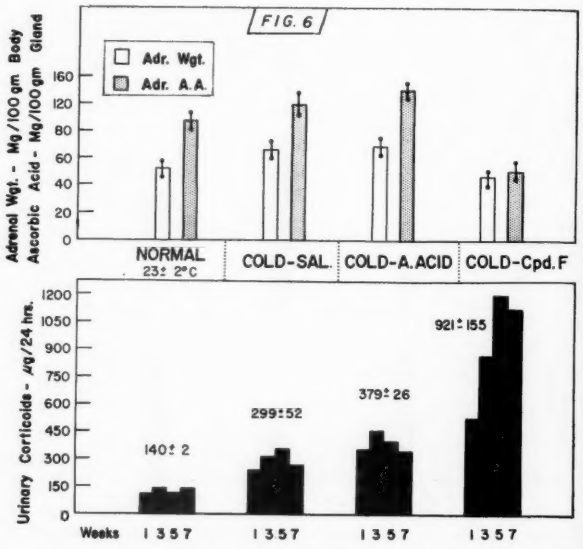


FIG. 6. Effect of ascorbic acid and compound F on adrenal gland function at low temperatures (7 ± 2°C). Upper graph depicts mean adrenal-body weight ratio (*open bar*) and ascorbic acid concentration in the gland (*stippled bar*), with S.E.M.'s (*vertical lines*), in guinea pigs at room temperature and in the cold. Urinary corticoid levels, expressed as μg of compound F excreted per guinea pig per 24 hr., are shown in the lower graph. Determinations were made on pooled urines from 6–10 animals using a modified Porter-Silber method. Numbers above columns represent the over-all mean corticoid excretion (±S.E.) for the 7-wk. period of cold exposure.

adrenal hypertrophy characteristic of cold. Contrariwise, hydrocortisone administration in parallel experiments (12.5 mg subcutaneously, daily for 46 days) inhibited the adrenal enlargement and significantly reduced ascorbic acid concentration in the gland. Adrenal-body weight ratios in cold-exposed animals receiving saline and ascorbic acid were 64.1 ± 3.0 and 67.6 ± 3.5 respectively. With hydrocortisone, the adrenal-body weight value (49.3 ± 4.9) was close to that of room temperature controls (52.2 ± 2.4). The relatively high amounts of exogenous hydrocortisone needed to inhibit the adrenal hypertrophy may indicate that the turnover rate of adrenocortical hormone, like thyroid hormone, is accelerated in chronic exposure to cold. The feed-back mechanism, nevertheless, appears to be operative at low temperatures. These results do not entirely conform with those of Dugal and Thérien (13) who found that ascorbic acid in large doses completely prevented adrenal enlargement in guinea pigs and rats chronically exposed to moderately cold temperatures (2°–4°C). Survival of rats in a cold room (244 days) was clearly favored by administration of the vitamin. Inasmuch as growth and survival of animals in the present experiments were good, any beneficial effects ascorbic acid may have had on these processes were not discernible. The failure of ascorbic acid, however, to affect adrenal gland function at slightly higher temperatures makes it doubtful that the physiologic effects of the vitamin in cold acclimation are exerted through pituitary-adrenal interplay.

HYPOTHALAMIC-HYPOPHYSIAL MECHANISMS

Although chronic exposure of the guinea pig to moderately low temperatures results in a sustained augmentation of thyroid and adrenal function, the rapidity with which the pituitary TSH and ACTH mechanisms are activated by neural 'stimuli' has not been determined. Nor is it known whether the heightened pituitary function, once established, requires continued hypothalamic mediation. The experimental difficulties involved in complete dissociation of neural and hormonal components in cold acclimation are major; inferences made from studies on one rodent cannot be applied indiscriminately to another. Massive release of pituitary TSH can be demonstrated within 1 hour or less of acute cold exposure in both hamster (14) and rabbit (15); exogenous thyroid hormone prevents the TSH discharge in the former animal but is relatively ineffective in the latter. In the rat, hypothalamic lesions which curtail pituitary TSH secretion do not interfere with vigorous release of the hormone in propylthiouracil-treated animals and do not hinder its rebound in the adenohypophysis to supranormal levels after goitrogen withdrawal (16). It is clear that wide excursions in levels of TSH secretion can occur despite hypothalamic deficit and that the capacity of the pituitary for rapid and massive release of thyrotrophin is not limited to a cold stimulus. Interpretation of the early neuroendocrine events which ensue at low temperatures is further complicated by apparent differences in pitui-

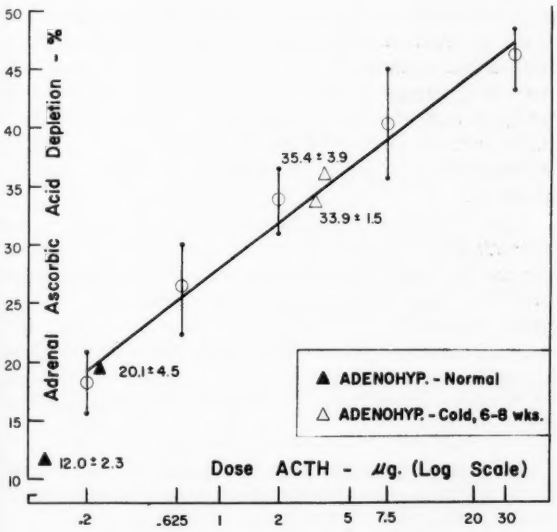


FIG. 7. Pituitary ACTH in cold-exposed guinea pigs. The regression line (*open circles*, 6–10 rats per point) describes the mean % depletion of ascorbic acid in the right adrenal of 5–10-day hypophysectomized male rats obtained with a standard ACTH preparation (La-1-A). The method employed was basically that of Sayers *et al.* (27) with some modification. The % depletion of ascorbic acid in the right adrenal obtained with 1 mg and 0.5 mg equivalent of pituitary extracts from cold-exposed rats was 35.4 ± 3.9 and 33.9 ± 1.5 repectively. With anterior pituitary from rats at room temperature, corresponding values for ascorbic acid depletion were 20.1 ± 4.5 and 12.0 ± 2.3%. The differences are highly significant ($P < .01$).

tary TSH response to the degree of cold. Moderately low temperature is a more potent stimulus to activation of the pituitary-thyroid system of rat (2) and rabbit (17) than is intense cold; a finding which some investigators attribute to inhibition of TSH function by unduly high levels of adrenocortical hormone following the nonspecific stress (18). This explanation may be too facile. Adrenocortical influence on early thyroidal responses in cold exposed hamsters was negligible (19); moreover, there are instances in which cortical hormone may potentiate TSH secretion in the rat (20).

Whatever may prove to be the fundamental relationship between the thyroid and the adrenal in acute exposure to cold, it is quite clear that for the guinea pig augmentation of TSH and ACTH pituitary function exists simultaneously for weeks during prolonged stay at low temperature. These pituitary activities may take higher priority in cold acclimation of the guinea pig than for other rodents, particularly those which are hibernators. Knigge (21) found cytological changes indicative of increased adrenocortical activity but no adrenal hypertrophy in female hamsters exposed to a temperature of 5°C for 15–60 days. Thyroidal radioiodine uptake was appreciably elevated throughout but the gland underwent morphological changes generally associated with diminished rather than increased function. Thyroidal activation and adrenal hypertrophy frequently coexist in the refrigerated rat but there is some question here as to whether high levels of corticosterone production are maintained by the enlarged adrenal (22), and the suspicion has been voiced that the character of steroids formed may eventually change.

It is experimentally feasible by electrocautery to interfere with the functional activity of one pituitary-target gland system in the cold-exposed animal and leave the other relatively unaffected. In guinea pigs bearing small ventral hypothalamic lesions, a 65 day exposure period to 5°C resulted in a diminution of the level of corticoid excretion from peak values in refrigerated controls; the histologic response of the thyroid gland did not correlate well with the change in adrenal function. Converse effects on pituitary-target gland functions were found in rats with lesions in the preoptic and anterior hypothalamic areas of the brain. This type of lesion typically produced persistent estrus, follicular ovaries and hypertrophied uteri. No significant change in the functional status of the pituitary-thyroid system was seen in persistent-estrus lesioned rats at room temperature for 2–5 months. Upon subsequent exposure to a temperature of 5°C for periods of 12–52 days, however, the acceleration of radioiodine release and histologic activation of the thyroid characteristic of sham-operated and intact refrigerated controls did not occur (23). In contrast, adrenal hypertrophy was substantial and of about equal degree in both lesioned and control animals. The estrus vaginal smear found repeatedly in operated rats at room temperature was replaced by a smear of the diestrus type; ovarian atrophy and uterine involution were marked. Chronic exposure to cold was well tolerated by rats bearing lesions in the preoptic area. Survival of rats was poor in those with severe median eminence lesions. The impairment which may have occurred in the temperature regulating mechanisms in both anterior and posterior hypothalamus was not assessed. The importance of an intact hypothalamus for augmentation of TSH secretion to a cold stimulus in the rat, and in the hamster (24), is re-emphasized. The capacity for adrenal hypertrophy to occur in other chronic stresses despite extensive hypothalamic destruction has been pointed out (25). The regressive nature of the changes which ensue in the reproductive tract of the cold-exposed lesioned rat shows how precariously balanced pituitary gonadotrophin secretion must be when the hypothalamus is tampered with experimentally.

SUMMARY AND CONCLUSIONS

The endocrine adjustments made by guinea pigs chronically exposed to moderately low temperatures were characterized by a sustained augmentation in function of the pituitary-thyroid and adrenal systems. Activation of TSH and ACTH mechanisms was associated with profound cytologic change in the basophil cells of the adenohypophysis. Enhanced synthesis of the pituitary protein hormones was not reflected in S^{35}-methionine accumulation in the adenohypophyses of either rat or guinea pig

although thyroidal uptake of the labeled amino acid did increase in the former. In both species rates of release of I^{131}-labeled thyroid hormone were accelerated in the cold. Other parameters of pituitary-thyroid function indicated that the increased tempo of thyroid hormone secretion was counterbalanced by increased utilization and disposal of the hormone at the periphery. Adrenal function was also enhanced by the cold stimulus as signified by hypertrophy of the adrenal gland, elevated levels of corticoid excretion and very high ACTH concentrations in the pituitary. Hydrocortisone administration inhibited adrenal enlargement in the cold-exposed guinea pig and reduced ascorbic acid concentration in the gland, suggesting that the feed-back mechanism was still operative at low temperatures. The results of ascorbic acid administration in high doses gave no support to the concept that the vitamin either substitutes for adrenocortical hormone or conditions the pituitary-adrenal interplay at low temperatures. Interference with the functional activity of one pituitary-target gland system in the cold, leaving the other relatively unaffected, was accomplished by electrocautery of the hypothalamus. Ventral hypothalamic lesions in the refrigerated guinea pig moderated the rise in corticoid excretion, irrespective of thyroid function. In rats with preoptic and anterior hypothalamic lesions the anticipated increase in thyroid secretion rate was not elicited whereas the capacity of the adrenal to enlarge was unchanged.

The over-all results illumine the basic role of the rodent's adenohypophysis in cold acclimation. Appropriate trophic hormone responses to cold, triggered and probably maintained by neural influences, insure adequate production and delivery of thyroid and adrenocortical hormones to the circulation. These target gland hormones in turn promote the cold acclimation process by influencing cellular metabolism in ways not yet precisely determined.

The author is indebted to Dr. John J. Schneider of Jefferson Medical College, who made the urinary corticoid determinations in this study.

REFERENCES

1. Stevens, C. E., S. A. D'Angelo, K. E. Paschkis, A. Cantarow and F. W. Sunderman. *Endocrinology* 56: 143, 1955.
2. Williams, R. H., H. Jaffe and C. Kemp. *Am. J. Physiol.* 159: 291, 1949.
3. Rand, C. G, D. R. Riggs and N. B. Talbot. *Endocrinology* 51: 562, 1952.
4. Sellers, E. A. and S. S. You. *Am. J. Physiol.* 163: 81, 1950.
5. Cottle, M. and L. D. Carlson. *Endocrinology* 59: 1, 1956.
6. D'Angelo, S. A. *Pituitary Regulation of Thyroid Gland Function. The Thyroid.* Brookhaven Symposia Reports. No. 7:9, 1955.
7. Dempsey, E. W. and E. B. Astwood. *Endocrinology* 32: 509, 1943.
8. D'Angelo, S. A. *Endocrinology* 53: 331, 1953.
9. D'Angelo, S. A. and R. E. Traum. *Ann. New York Acad. Sc.* 72: 239, 1958.
10. Levey, H. A. and S. Roberts. *Am. J. Physiol.* 189: 86, 1957.
11. Boatman, J., J. H. Sunder and C. Moses. *Fed. Proc.* 10: 16, 1951.
12. Melchior, J. B. and M. N. Halkis. *J. Biol. Chem.* 199: 773, 1952.
13. Dugal, L. P., and M. Thérien. *Endocrinology* 44: 420, 1949.
14. Knigge, K. M., D. H. Solomon and S. M. Bierman. XXI *Internat. Physiol.* Congress, 1959, p. 146.
15. Bottari, P. *Ciba Foundation Colloquia on Endocrinology* 11: 52 1957.
16. D'Angelo, S. A. *J. Endocrinol.* 17: 286, 1958.
17. Brown-Grant, K., C. von Euler, G. W. Harris and S. Reichlin. *J. Physiol.* 126: 1, 1954.
18. Brown-Grant, K., G. W. Harris and S. Reichlin. *J. Physiol.* 126: 41, 1954.
19. Knigge, K. M., R. S. Goodman and D. H. Soloman. *Am. J. Physiol.* 189: 415. 1957.
20. D'Angelo, S. A., C. E. Stevens, K. E. Paschkis and A. Cantarow. *Proc. Soc. Exper. Bio. & Med.* 83: 181, 1953.
21. Knigge, K. M. *Anat. Rec.* 127: 75, 1957.
22. Schönbaum, E. (This Symposium) *Fed. Proc.* 19, Suppl. 5: 85, 1960.
23. D'Angelo, S. A. Abstr. 1st Internat. Congress of Endocrinology, 1960.
24. Knigge, K. M. and S. M. Bierman. *Am. J. Physiol.* 192: 625, 1958
25. D'Angelo, S. A. *Endocrinology* 64: 685, 1959.
26. D'Angelo, S. A. and A. S. Gordon. *Endocrinology* 46: 39, 1950.
27. Sayers, M. A., G. Sayers and L. A. Woodbury. *Endocrinology* 42: 379, 1948.

Discussion

E. SCHÖNBAUM, K. M. KNIGGE, N. PACE, R. S. GORDON, JR., S. A. D'ANGELO, E. D. P. De ROBERTIS, E. F. ADOLPH, W. M. BOOKER, E. J. MASORO

Dr. Schönbaum: Mr. Chairman, I wonder whether Dr. Knigge or perhaps some of the other authorities present would comment on what is considered to be the minimum dose of thyroxine needed by the rat for survival in the cold. I believe the reported data vary considerably.

Dr. Knigge: Dr. Schönbaum's question is a difficult one because he asks the minimum dose required for survival. Experiments such as those of Dempsey and Astwood, Woods, and Carlson and Cottle, were designed to demonstrate the actual amounts of thyroid hormone being secreted. These amounts of hormone are undoubtedly not equivalent to the minimum required for survival. The explanation for the

varied estimates of thyroxine secretion during cold exposure of the rat appears to be related to differences in the degree of cold exposure, time after exposure at which thyroid function is measured, technique of measurement, pretreatment, diet, and possibly strain of the animal used. Thyroidectomized rats can survive cold exposure if initially administered doses of thyroxine somewhat greater than their control pre-exposure output; as the period of cold exposure increases, the requirement for thyroxine may decrease.

Dr. Pace: In view of Dr. Hart's comments this morning, I would like to ask how similar is the hamster to the rat. The hamster appears to behave quite differently, in many respects, in terms of its general response to cold exposure.

Dr. Knigge: Although there are some differences, the rat and hamster exhibit both acute and chronic responses to cold exposure. The acute response, which we believe to be influenced primarily by neural mechanisms, is demonstrated easily in the hamster. In the rat, acute cold exposure may evoke either thyroid or adrenal activation depending, apparently, upon the temperature. If an acute adrenal response is elicited by the proper degree of cold, a thyroid response may be inhibited by the resulting high levels of steroids. With regard to chronic exposure, the hamster does exhibit increased thyroid function during the period of cold exposure prior to its entrance into hibernation.

Dr. Gordon: I should like to suggest one possible, if unlikely, explanation for the apparent paradox in the results of measurement of thyroid function. It has been reported that in the first 12 hours of cold exposure animals show a rapid increase in the rate of I^{131} release from the thyroid, but no increase in serum PBI levels. This might be expected to occur if there were an abrupt decrease in the amount of circulating thyroxine-binding proteins leaving more of the plasma thyroxine in the freely diffusible form. An increased supply of thyroid hormone from the gland could then be balanced by an increased rate of removal of the plasma with no need for increase of the serum PBI. Levels of thyroxine-binding protein can be measured by appropriate techniques and it might be worthwhile to see if there is any alteration. If there were, one would then have to find a way whereby the stress of cold exposure could alter the concentration of a plasma protein which, as far as is known, is not under the control of any of the endocrine glands whose function we have been discussing.

Dr. Knigge: In these experiments we measured PBI only up to four hours of cold exposure since acceleration of thyroidal I^{131} occurred after that time and it was concluded that no major change in the circulating PBI was responsible for initiating this release phenomenon. After 4 hours of cold exposure the release of thyroidal hormone was readily detectable by radiometric measurement and thyroidal I^{127} content decreased approximately 30%. The hamster thyroid weighs approximately 5 mg and contains 15 μg I^{127}/100 mg. PBI values average 2.8 μg %. The actual amount of iodine released by the gland is, therefore, small and is either not detectable as a rise in PBI or is compensated for by an equivalent increase in rate of removal from the plasma. Measurement of thyroxine-binding protein may yield additional information about the nature of this response.

Dr. D'Angelo: The possibility should be mentioned that even in the acute phase, say within several hours, some thermogenesis results which in turn could influence disappearance rates of TSH from the blood. We have shown in hypophysectomized rats that the slow rate of removal of TSH from the circulation is greatly enhanced if the metabolic rate is previously elevated by thyroid hormones. Measurement of TSH blood levels in the hamster experiments would have been highly informative.

Dr. De Robertis: I was very interested to hear about this latent period that Dr. Knigge has found in the release of hormone from the thyroid gland under stimulation by TSH. In 1941 we showed that injection of TSH produces a reaction in the thyroid gland in as early as 10 minutes. The total cytological reaction was in two phases, the first ending in about 1½ hours, during which we thought that the synthesized material was being released in the follicles. On the contrary, the release was actually very high 3 or 6 hours after the injection of TSH.

Dr. Adolph: I would like to comment on a point which was brought up as to whether we can make a distinction between cold exposure and hypothermia. It seems to me that these two overlap so much that it is improper to think of them as separate phenomena. You cannot cold-expose even one of Dr. Keller's dogs without having hypothermia in some tissues, because the superficial tissues are hypothermic. We actually tested this matter in golden hamsters and in ground squirrels to see whether we could get adaptation to cold more rapidly, as measured by the rate of body cooling, *a)* when we allow the central core of body temperature to fall or *b)* when we did not allow it to fall by merely exposing the animals to cool air (*J. Appl. Physiol.* 9: 53, 1956). The central body temperature, when it fell rapidly, produced the signs of adaptation in much fewer exposure hours than when the animal was placed in conditions in which the core remained at the usual temperature and only the superficial tissues cooled. It seems to me, therefore, that when we talk about cold exposure we are also talking about a degree of hypothermia.

Dr. Booker: The work of Dr. D'Angelo is certainly exciting and challenging. I should like to have him expand his ideas a little further as to the picture he is obtaining in what I should call 'chronic stress.' For example, he mentions a situation in which the levels of ACTH, ascorbic acid and adrenocortical hormone are all elevated. As you know, in acute stress the adrenal ascorbic acid falls when the ACTH level rises, and upon the increase of the ACTH level and the stimulation of cortical hormone secretion, ACTH reaction is cut off. His work may show the delineation between acute and chronic stress.

I should like to say also that we have observed, as I remember our experiments, that ascorbic acid does not decrease the size of the adrenal gland in the rat, which agrees with the findings reported here for the guinea pig.

Dr. D'Angelo: We have not studied adrenal response in acute cold exposure. Without minimizing the role of the hypothalamus in the ACTH mechanism, I feel that in the rat the adenohypophysis has a high measure of residual ACTH function which may even be augmented in certain chronic stresses, starvation or chronic thyroid hormone treatment, for example. Although it is reasonably certain that the quick precipitous response that Dr. Knigge mentioned needs a neural mechanism, it is not yet established just how much of the increased ACTH secretion in cold acclimation represents augmented basal activity and what proportion, if any, results from continued hypothalamic participation. The failure of ascorbic acid administration to affect adrenal size in the guinea pig and the rat stands in contrast to the positive findings of Dugal and Thérien (*Endocrinology* 44: 420, 1949) in both species. Their results were more impressive in the rat, especially with respect to survival, than in the guinea pig. They used slightly lower temperatures in their experiments while we used higher doses of ascorbic acid. Concerning the point about the servomecha-

nisms between adrenal and anterior pituitary in chronic cold exposure, it is difficult to say why the high levels of corticoids produced do not inhibit the ACTH mechanism. I must point out here that we did not measure the blood levels. The increased corticoid excretion over various time periods certainly reflects increased disposal as well as production of the hormone; like thyroid hormone, rates of production and utilization of cortical hormones may be balanced so that levels in the blood are nearly normal and thus would not interfere with continued secretion of ACTH. It is also possible that with chronic cold, the sensitivity of the pituitary itself to cortical hormone may change. It did take a relatively large amount of exogenous hydrocortisone to inhibit the adrenal hypertrophy.

DR. MASORO: The reason for your use of sulfur-labeled amino acids as a measure of energetics is not clear to me. Your intention to use tritium-labeled thymidine for the same purpose is also unclear to me; I wonder if you would go more into your reasons for using these methods for the study of bio-energetics.

DR. D'ANGELO: I was pointing out that there is really little information about metabolic enzymatic changes in the hypophysis which may be related to the secretion of the pituitary protein hormones. We used the radiometric approach to learn whether the accumulation of labeled amino acids in the gland might parallel the enhanced protein synthesis. Inasmuch as no method has been devised which measures directly the rates of formation and release of a trophic hormone, such an approach, however unrewarding for the moment, may offer clues.

DR. MASORO: Would it not be possible for you to use more conventional methods for measuring energy metabolism? I feel that biosynthetic activities are not a good measure of energy metabolism because they can be controlled by specific mechanisms that in no way serve as an index of total energy metabolism.

DR. D'ANGELO: The reasons why the energy metabolism of pituitary was not studied directly are: first, some lack of competence with biochemical tools and, second, some discouragement from the literature on the subject itself. Biochemists have devoted much time to the isolation and identification of the pituitary principles. Metabolic studies on the gland are sparse. In an excellent study, Levy and Roberts (*Am. J. Physiol.* 189: 86, 1957) found that enzyme levels, glucose utilization, lactate production and oxygen consumption in the pituitary did not correlate well with synthesis and release the adenohypophyseal hormones. I thought I would try a different approach.

Most of us in endocrinology seriously engaged in radioisotope work are aware of the pitfalls of interpretation. What is needed in this type of study is a method which can measure *in vivo* synthesis and release of pituitary hormones, simultaneously, without sacrificing the animal or removing its pituitary and mincing it. As to the suggestion about autoradiographic studies, I agree that much may be gained from them and efforts along this line with tritiated thymidine are being made.

DR. SCHÖNBAUM: I would like to introduce the role of the liver into this discussion. Yates and colleagues in Boston have shown that there is a close relationship between thyroid function, adrenal size, and the ability of the liver to reduce Δ 4-3 ketone of the corticosteroids. Yates, *et al.* (*Endocrinology* 64: 816, 1959) suggest the possibility of a feed-back mechanism whereby the activity of the liver could, in part, influence pituitary function. Dr. D'Angelo may not have been able to observe these changes with the particular method he used. Also, I would like to ask Dr. D'Angleo whether administration of the rather large doses of the steroid to guinea pigs might have introduced a partial functional hypophysectomy. Consequently, after some time, adrenal ascorbic acid concentration may have decreased, as he observed. Further, we have not yet heard much about the effects of exposure to cold in the dog. In anesthetized dogs, Eik-Nes (*Fed. Proc.* 14: 336, 1955) failed to obtain increased steroid levels on exposure to 5°C. Hume, Egdahl and their collaborators carried out a large number of studies of adrenal cortical function in unanesthetized dogs. A cannula was introduced into the adrenal vein; after a recovery period of 24 hours or longer, the dogs were exposed to a variety of experimental conditions. Samples of adrenal venous blood were collected and the rates of secretion of 17-hydroxycorticosteroids determined. Exposure of dogs to -10°C for periods as long as 30 hours did not appreciably increase the output of corticosteroids (Nelson *et al. Endocrinology* 58: 309, 1956), although exposure to even lower temperatures ($-46°$ to -79°C) did cause a significant rise in the steroid levels. This response persisted for only 1–3 hours; none of the dogs became hypothermic (Egdahl and Richards. *Am. J. Physiol.* 185: 239, 1956). It is regrettable that we are not able to perform this type of experiment in the rat.

DR. D'ANGELO: The liver may influence thyroid function indirectly through an interhepatic circulation of iodine. Its chemical effect on circulating steroids, especially estrogens, is well known; I do not see any good evidence, however, that the liver is specifically implicated in the pituitary-thyroid or adrenal feed-back mechanisms. We were unable to find substantial change in thyroid function during hepatic regeneration in the rat. Changes in liver function would have to be drastic to explain the magnitude of the response for the pituitary adrenal system. Probably all tissues in the body have some indirect influence on circulating levels of cortical hormones, either through utilization or inactivation. The contribution to this effect by the liver mass would naturally be high. The reason why adrenal ascorbic acid was reduced after hydrocortisone treatment is not clear to me; adrenal weight values were not at the hypophysectomy level. Perhaps the change was spurious rather than real; hydrocortisone caused some body weight loss. Guinea pigs are rather sensitive to starvation and because they do not synthesize Vitamin C, a day or two of inanition could drive down adrenal ascorbic acid concentrations substantially. This phase of the study clearly needs more investigation. The comment by Dr. Schönbaum about the unimpressive changes in corticosterone blood levels of dogs at low temperatures serves to re-emphasize the point that different species, though possessing in common the basic homeostatic mechanisms, differ in the levels at which the homeostasis is pitched. The guinea pig has a large adrenal relative to the body weight; its pituitary ACTH mechanism seems easily aroused by a variety of stresses such as cold or starvation, and adrenal hypertrophy in this species can be quite marked, yet its pituitary-thyroid function is normally at a low ebb. TSH levels in blood and hypophysis are relatively low and the thyroid is histologically inactive. In the rat, a closely related rodent, the thyroid normally is on the verge of hyperplasia and TSH levels in both blood and pituitary are much higher. It is possible, experimentally, to bring the level of pituitary-thyroid activity in one species to that of the other. Insofar as the cold stimulus is concerned, it would appear that the guinea pig is well suited as the experimental animal since the intensity or 'flare-up' of the ACTH and TSH functions in the pituitary enable a clearer view of mechanisms which may be basic to other species even though operating at lower intensity.

Role of thyroid secretion in cold acclimation

WALTER H. COTTLE
Department of Physiology and Pharmacology, University of Alberta, Edmonton, Canada

COTTLE, W. H. *Role of thyroid secretion in cold acclimation.* Fed. Proc. 19, Suppl. No. 5: 59–63. 1960.—Reviewed briefly are a number of experimental studies designed to evaluate thyroid secretion rate and its control during cold acclimation in small mammals. The possible role of the hormone in the process of acclimation is discussed. The suggestion that the increased resting metabolism of cold-acclimated animals is a product of the augmented thyroid secretion in the cold is untenable. Evidence is presented against the possibility that augmented thyroid secretion is prerequisite to development of the altered thermogenesis characteristic of cold acclimation.

I AM SURE THERE ARE MANY AMONG YOU who are much better qualified to speak on the subject of thyroid function than I, and it is therefore with some trepidation that I proceed. What I have to say is more of the nature of a short review on the possible relationship of thyroid function to cold acclimation, rather than a discussion confined to my own research.

Thyroid hormone by its nature appears to be related to the changes seen in small homeotherms upon chronic cold exposure. Beyond this, if one were to ask what the role of thyroid hormone is in the process of cold acclimation, my answer would be "I don't know."

Most studies aimed at this problem can be grouped according to which of three questions they attempt to answer:

1) Is thyroid secretion rate increased by cold exposure and if so, how much?

2) What are the controlling mechanisms through which the cold stimulus acts to alter secretion?

3) What happens to the acclimation processes if we experimentally manipulate thyroid status?

Morphological changes in the thyroid have been seen in a number of species following prolonged cold exposure. These changes include an increase in gland weight (1, 2), increased vascularity (3), and decreased colloid within follicles (4, 5). Except for the last, each of these changes is a recognized criterion of increased function of glandular tissue. Of course, altered function of the thyroid may not be reflected in a weight change, as changes in the amount of colloid, condition of the secretory epithelium, and vascularity may not be parallel.

There is some evidence that thyroid activity in rats reaches a maximum with about 3 weeks exposure to cold and returns to near normal condition after 6–10 weeks. Starr and Roskelley (6) found the height of the follicular cells in thyroids from rats kept at 15°C reached a maximum in about 3 weeks and returned to near normal in about 6 weeks.

Heroux and co-workers (7) did not find histological evidence of increased thyroid function in rats kept 3 months outdoors in winter conditions. These rats, on the other hand, had developed the same degree of cold resistance as animals kept in the cold under laboratory conditions.

Estimates of the amount of thyroid hormone secreted by rats have indicated those at 5°C produce about twice as much as those at 25°C. Dempsey and Astwood (8) blocked thyroid function in rats with propylthiouracil, then administered a series of graded doses of thyroxine to various groups. After 14 days animals were killed and the glands removed and weighed. From the gland weights they were able to determine the dose of thyroxine which would maintain the normal thyroid weight. This gave an estimate of hormone production at different temperatures. These were 9.5 Hg at 1°C, 5.2 at 25°C and 1.7 at 35°C. This method has been criticized by van Middlesworth *et al.* (9), who have found propylthiouracil enhances the effect of thyroid stimulating hormone (TSH). Woods and Carlson (10) estimated the amount of thyroxine required to restore resting metabolism of thyroidectomized rats to the level of that of intact rats. They concluded secretion at 5°C to be equivalent to 7.5 μg of L-thyroxine, and at 25°C, 3.5 μg. Requirement was still more than double after 60 days at 5°C.

Measurements of thyroidal radioactivity at various periods after administration of radioactive iodine (I^{131}) is used widely as an assay of thyroid function. Uptake by the thyroids of rats kept 1–3 weeks at 4°C and measured 2 hours after injection of the isotope has been found to be greater than in rats kept at room temperature (11). After 6 weeks, 2-hour uptake was found similar to that of controls. This decreased uptake appears to confirm the histological picture.

Radioactive iodine is lost more rapidly in the urine of cold-exposed rats than in normals. It appears that although the thyroid actively traps iodide, it also leaks out. The result is that 24- and 48-hour uptake counts show less I^{131} in glands of cold-exposed animals than of controls (12). Less of the I^{131} administered finally becomes bound in the gland. The changes in this very dynamic process have not been well illustrated.

A number of studies have evaluated thyroid function by measuring serum levels of the hormone (protein-bound iodine, or PBI). The level in the blood represents

a steady state condition and, if regulation is sensitive, a change in turnover rate of the hormone may not be seen as a change in the level. Bondy and Hagewood (13) reported that serum PBI in rats drops on initial exposure to cold but is essentially back to normal levels in 72 hours. Measurements made after longer exposures have been inconsistent. There have been reports of a slight decrease in rats after 2 weeks exposure to 5°C (2), of no change (14), and of a slight increase (15).

The finding that administered I^{131}–tagged hormone disappears more rapidly from the blood of cold-acclimated rats than from that of warm-acclimated animals (16) suggests a more rapid utilization by the former. This may be due to more rapid loss in the feces. Intoccia and van Middlesworth (17) have reported that labeled hormone administered to rats is lost more rapidly in the feces by animals in the cold than by those in the warm. They suggest that the increased dietary bulk, which results from cold exposure, facilitates loss of hormone in the feces and thereby increases requirement in the cold.

The rate of hormone secretion by the thyroid can be evaluated conveniently by following the biological decay of radioactivity over the thyroid following administration of I^{131}. Endogenous hormone formed in the gland is labeled by the tracer amount of the isotope which is injected. With rats, initial counts are made 24 or 48 hours later. Repeated counts at some convenient interval, usually every 24 or 48 hours, for periods up to about 1 week indicate the rate of release. Dr. D'Angelo spoke about this method yesterday. Cold-acclimated rats tested in this manner show a more rapid release of hormone than do warm-acclimated animals (12). Dr. Knigge has shown that the accelerated release is evident within 3 hours in the hamster. Brown-Grant (18) found exposure in rabbits to a moderate degree of cold resulted in an increased rate of release within 8 hours. Acute exposure to more severe cold resulted either in no change or in a decrease. Probably this more severe condition acts as a nonspecific stress which reduces TSH release.

It is well recognized that acclimation of small homeotherms to cold is associated with an increase in the metabolic rate measured at a neutral temperature. This rate can be termed the resting metabolism. The increase resembles that produced by administration of thyroxine and has led some to assume the two conditions analagous. I will point out why this may not be so in a few minutes. The increased resting metabolism is reflected in an enhanced metabolism of various tissues, particularly liver, measured *in vitro* (18a). This resembles again the condition in hyperthyroid rats.

Mechanisms controlling secretion of the thyroid were discussed in some detail yesterday. I will discuss this question briefly and I apologize for obvious repetition.

There is good evidence that the increased thyroid activity in the cold is brought about through release of thyroid stimulating hormone (TSH) by the adenohypophysis. Thyroids of hypophysectomized animals exposed to cold do not show the evidence of increased thyroid secretion seen in intact animals (5, 19). Basophil cells, believed responsible for production of TSH are numerous and are hypertrophied in pituitaries removed from cold-acclimated rats (20). Finally, TSH in serum of cold-exposed animals is more readily detected than in serum from controls (14, 20).

The mechanism through which the cold stimulus operates to bring about release of TSH is not settled. That the stimulus acts through direct innervation of the adenohypophysis via the hypothalamo-hypophyseal tract appears unlikely because of lack of visible neural connections. Indeed Uotila (21) sectioned the pituitary stalk in guinea pigs and reported cold-induced changes in the thyroid were abolished. Barnett and Greep (22) have reported a limited response from such an experiment. The possibility of damage to blood vessels, etc., which in turn would affect pituitary function, makes interpretation of these studies difficult. A further suggestion, made by Rand and co-workers (2), was that a slight drop in circulating level of thyroid hormone resulting from increased hormone utilization causes a compensatory release of TSH. Later evidence has suggested that such a feed-back mechanism might function to maintain the normal circulating level of thyroxine but that stimuli like cold which augment thyroid function might depend on the normal hypothalamo-hypophyseal relationship. This is indicated by findings that hypophysectomized rabbits (23) and hamsters (19) bearing pituitary grafts have been found to have a normal rate of thyroidal I^{131} release at room temperature but lacked the augmented rate when exposed to low temperatures. Likewise, hamsters with lesions interrupting the hypothalamo-hypophyseal connections also did not show the accelerated release of I^{131} in the cold.

Experiments in which the thyroid status of animals in the cold has been manipulated have not only given some suggestions regarding the role of the thyroid, but have also raised a number of questions.

Thyroidectomized rats, or rats given propylthiouracil to block thyroid function, survive only a few days at low temperatures. If thyroidectomy is performed after acclimation, animals will survive much longer (1). Why thyroid hormone is essential during development of acclimation and is less so during its maintenance remains unanswered.

At least a portion of the increased resting metabolism of cold-acclimated animals is not a product of increased thyroid secretion. Sellers and You (1) found thyroidectomized rats given a small daily replacement dose of thyroxine could be maintained at 1.5°C indefinitely. In addition, the metabolic rate of these animals, measured either at 1.5°C or at 30°C, showed a gradual increase much like that of normal animals. This can be seen in figure 1. A similar increment in resting metabolism can be seen in the data of Woods and Carlson (10). In figure 2, one can see that at any dose level of thyroxine the metabolic rate of the cold-exposed animals is higher than that of controls. Whether or not animals deficient

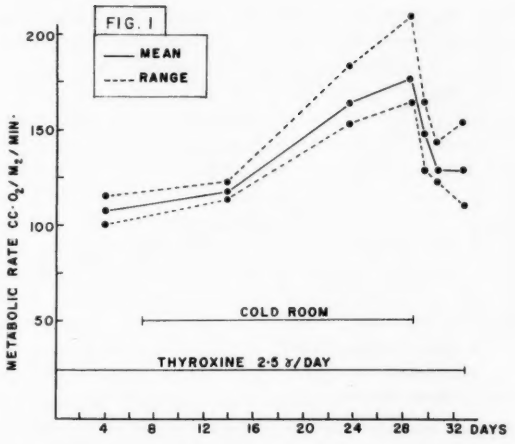


FIG. 1. Resting metabolism ($MR^{30°C}$) of four thyroidectomized rats fed propylthiouracil and given a small replacement dose of thyroxine daily (2.5 μg) before, during and after exposure to cold. From Sellers and You (1).

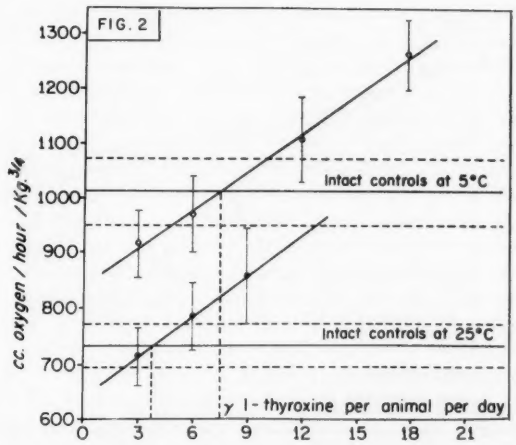


FIG. 2. Thyroxine requirements of animals kept 14 days at 5°C and of comparable animals kept at 25°C, measured by O_2 uptake response ($MR^{25°C}$, resting metabolism) to thyroxine by thyroidectomized rats. *Solid circles* represent animals kept at 25°C. *Open circles* represent those kept at 5°C. *Vertical bars*, indicate ±1 S.D. From Woods and Carlson (10).

in thyroid hormone develop the enhanced cold resistance while in the cold has not been adequately tested.

The augmented resting metabolism may be secondary to the greater food intake in the cold. Possibly it merely reflects the greater specific dynamic action of food arising from the larger quantity of food eaten. This has been concluded by Mitchell and Edman (24) from experiments in which restriction of food to acclimated rats depressed resting metabolism. However, many workers have found resting metabolism is still elevated after 24 hours fasting. This appears to rule out specific dynamic action.

Thyroid function is affected by the level of food intake. Reichlin (25) has demonstrated that the rate of release of tagged hormone (biological decay) is much reduced in rats by restriction of food. The rate of release of hormone during acclimation to cold is very much reduced by limited restriction of food (Cottle, unpublished observations). This can be seen in figure 3. In this experiment the amount of food allowed rats when placed in the cold was limited to that eaten by controls at 28°C. One can see that the rate of release is much slower than that for either controls at 28°C or those at 8°C. A difference between the two sets of controls is not evident. It appears that the stress imposed by restricting food depressed TSH production even below normal levels. The initial count here was made 15 days after the animals were placed in the cold room.

The increased food intake in the cold is not essential for development of the increased cold tolerance (Cottle, unpublished observations). As one can see in figure 4 such animals can maintain rectal temperature when tested by restraining and placing in a cold box. Ability to maintain temperature under these conditions is most likely due to augmented thermogenesis. Rats can thus

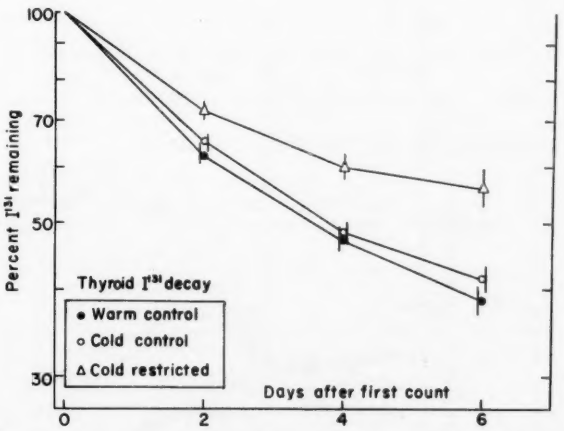


FIG. 3. The effect of limiting food available to rats during acclimation to cold on the release of I^{131} from the thyroid gland. Initial counts were made 15 days after animals were placed in cold. Food available to rats designated 'cold restricted' was limited to an amount equal to that eaten by controls at 28°C (warm control) beginning on the day they were placed at 8°C. Those designated 'cold control' were placed at 8°C at the same time and were given food without restriction. *Vertical bars* indicate ±1 S.E.

be acclimated to cold under conditions in which thyroid output is much reduced.

In contrast to this finding with food restriction is the observation that cold tolerance is not evident if acclimated animals are tested using survival without food at low temperature as the criteria (26). Under such conditions a more rapid depletion of energy stores by cold-acclimated animals is likely, which would offset any advantage of increased thermogenesis.

The increased thermogenesis in the cold-acclimated animal is most likely a product of the enhanced hormonal

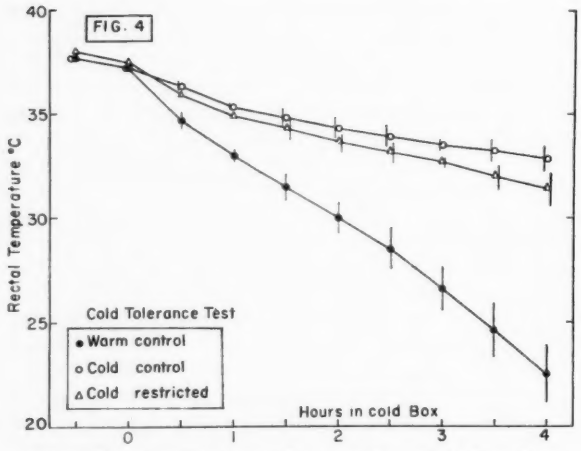


FIG. 4. Rectal temperatures of rats while restrained and exposed to cold. Food available to cold restricted animals was limited when placed at 8°C 3 weeks prior to the test. Groups are designated as in fig. 3. *Vertical bars* indicate ±1 S.E.

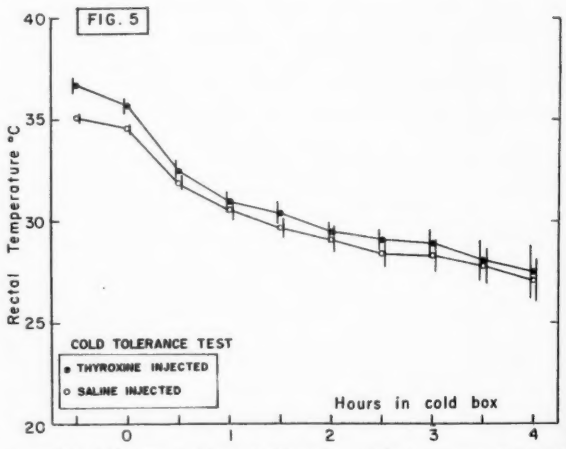


FIG. 5. Rectal temperatures of rats while restrained and exposed to cold. Animals designated 'thyroxine injected' were injected daily with 24 μg of L-thyroxine s.c. for 3 weeks. Controls (saline injected) received an equal volume of saline. *Vertical bars* indicate ±1 S.E.

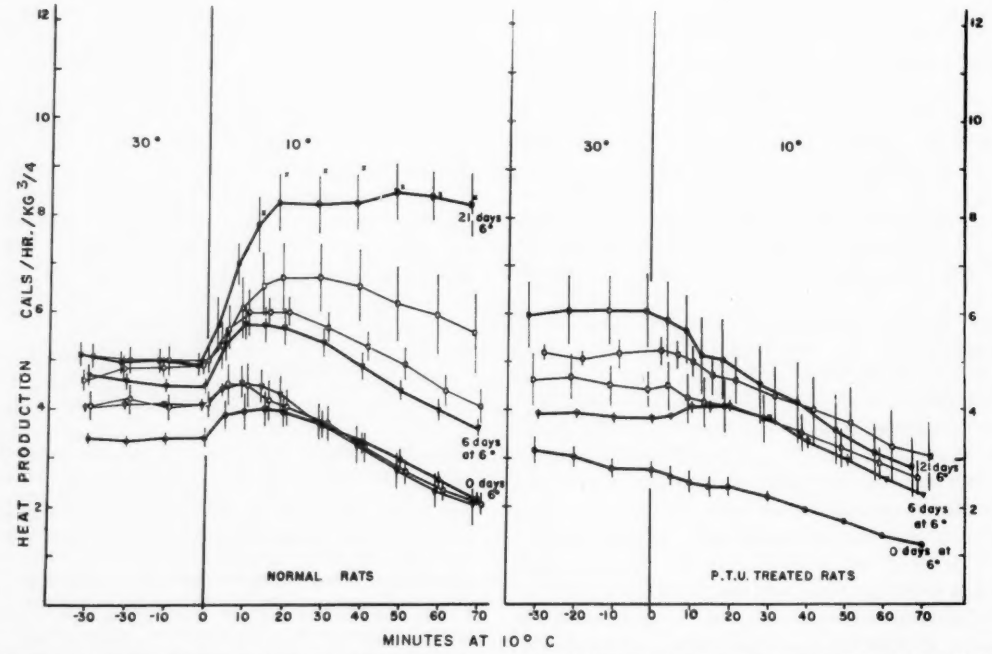


FIG. 6. Metabolic response of curarized rats on being transferred from 30°C to 10°C. Responses of normal rats are plotted on the left and of animals fed propylthiouracil on the right. Response of animals kept 0, 6 and 21 days are indicated by *solid circles*. *Open circles* represent intermediate exposures. *Vertical bars* indicate ±1 S.E.

or nonshivering control discussed at an earlier session. Apparently related to this is the observation that the calorigenic response to an administered dose of adrenaline is enhanced by prior cold acclimation. A similar enhancement can be produced by pretreatment with thyroxine. Ring (27) suggested that the increased thyroxine release in the cold brings about changes which enhance the calorigenic response to endogenous adrenaline released on exposure to cold. If this were so animals pretreated with thyroxine would be more cold resistant than normals. Sellers and co-workers (28) have found survival of rats under cold stress is not enhanced by such pretreatment. It also does not enhance cold resistance as tested by the more acute cold retraint test (Cottle,

unpublished observations). Figure 5 shows the rates of fall of rectal temperature of rats restrained at 5°C. These rats were treated with 24 μg of L-thyroxine daily for 3 weeks. A number of other pieces of evidence requires that Ring's hypothesis be modified before it will explain the metabolic changes seen with acclimation.

The role of the thyroid in this altered response is not clear. The enhanced thermogenesis does not seem to be related to the circulating level of thyroid hormone. Hsieh and Carlson (29) thyroidectomized rats previously acclimated to cold and followed the effect of the consequent levels of circulating thyroxine on the metabolic response of rats exposed to cold while curarized. This work was discussed by Dr. Carlson. Groups of animals were tested from 2 to 12 days post thyroidectomy. The maximal thermogenic response decreased progressively for 8 days, after which there was no further fall. The initial body temperature of the animals before testing was also found to be lower on each successive day after thyroidectomy. When the response was corrected for this fall in body temperature, the decrease in maximal thermogenesis no longer appeared significant. On the assumption that resting metabolism reflects circulating level of thyroxine, they concluded that the enhanced thermogenesis was not a direct product of the circulating level of thyroid hormone.

I would like to conclude by showing some data which appear to contradict the above conclusions. In an attempt to fix the level of circulating thyroxine on development of hormonal thermogenesis, propylthiouracil was fed to rats in the cold and a small dose (2 μg) L-thyroxine was injected daily. As can be seen such animals did not show the enhanced thermogenesis seen in the controls when tested under curare (fig. 6). The many lines represent different groups exposed to cold for different periods of time. The initial body temperature and metabolic rates of deficient animals were similar to those of control animals. (Values in this graph have not been corrected for the fall in rectal temperature which occurred during the test). The depression may have been due to the presence of the drug or one of a number of other factors. This experiment is only now being repeated using thyroidectomized as well as thiouracil-fed rats.

REFERENCES

1. SELLERS, E. A. AND S. S. YOU. *Am. J. Physiol.* 163: 81, 1950.
2. RAND, C. G., D. S. RIGGS AND M. B. TALBOT. *Endocrinology* 51: 562, 1952.
3. KENYON, A. T. *Am. J. Pathol.* 9: 347, 1933.
4. MILLS, C. A. *Am. J. Physiol.* 46: 329, 1918.
5. WOLF, O. AND R. O. GREEP. *Proc. Soc. Exper. Biol. & Med.* 36: 856, 1937.
6. STARR, P. AND R. ROSKELLEY. *Am. J. Physiol.* 130: 549, 1940.
7. HEROUX, O., E. SCHÖNBAUM AND A. DES MARAIS. *Fed. Proc.* 18: 67, 1959.
8. DEMPSEY, E. W. AND E. G. ASTWOOD *Endocrinology.* 32: 509, 1943.
9. VAN MIDDLESWORTH, L., G. JAGIELLO AND W. P. VANDERLAAN. *Endocrinology.* 64: 186, 1959.
10. WOODS, R. AND L. D. CARLSON. *Endocrinology.* 59: 323, 1956.
11. LEBLOND, C. P., J. GROSS, J. PEACOCK AND R. D. EVANS. *Am. J. Physiol.* 140: 671, 1944.
12. COTTLE, M. K. AND L. D. CARLSON. *Endocrinology.* 59: 1, 1956.
13. BONDY, P. K. AND M. A. HAGEWOOD. *Proc. Soc. Exper. Biol. & Med.* 81: 328, 1953.
14. STEVENS, C. E., S. A. D'ANGELO K. E. PASCHKIS, A. CANTAROW AND F. W. SUDERMAN. *Endocrinology* 56: 143, 1955.
15. SELLERS, E. A. In: *Cold Injury. Transactions of the Third Conference.* New York: Macy, 1955.
16. VAN MIDDLESWORTH, L. AND M. M. BERRY. *Am. J. Physiol.* 167: 576, 1951.
17. INTOCCIA, A. AND L. VAN MIDDLESWORTH. *Endocrinology* 64: 462, 1959.
18. BROWN-GRANT, K. *J. Physiol.* 131: 52, 1956.
18a. WEISS, A. K. *Am. J. Physiol.* 177: 201, 1954.
19. KNIGGE, K. M. AND S. M. BIERMAN. *Am. J. Physiol.* 192: 625, 1958.
20. BROLIN, S. E. *Acta Anat.* 3, Suppl.: 1, 1946.
21. UOTILA, U. U. *Endocrinology* 25: 605, 1939.
22. BARNETT, J. AND R. D. GREEP. *Am. J. Physiol.* 167: 569, 1951.
23. VON EULER, C. AND B. HOLMGREN. *J. Physiol.* 131: 137, 1956.
24. MITCHELL, H. H. AND M. EDMAN. *Nutrition and Climatic Stress.* Springfield: Thomas, 1951.
25. REICHLIN, S. *Endocrinology* 60: 470, 1957.
26. HART, J. S. *Rev. Canad. Biol.* 16: 133, 1957.
27. RING, G. C. *Am. J. Physiol.* 137: 582, 1942.
28. SELLERS, E. A., S. REICHMAN AND N. THOMAS. *Am. J. Physiol.* 167: 644, 1951.
29. HSIEH, A. L. AND L. D. CARLSON. *Am. J. Physiol.* 188: 40, 1957

Comparative effects of thyroxin in vivo and cold acclimation on metabolic activity of cell fractions from rat liver[1]

ROBERT E. SMITH
Department of Physiology, University of California School of Medicine, Los Angeles, California

EARLIER WORK IN THIS LABORATORY (1–3) and elsewhere (4, 5) has indicated that oxidative phosphorylation in particulate preparations from liver may be depressed in rats chronically exposed to lowered ambient temperature. Similar effects were noted much earlier (6–8) in thyrotoxic rats. Since increased thyroid activity has been repeatedly demonstrated by various means in cold-acclimated rats, e.g. (9–11), it was of interest to develop the comparison between subcellular effects of thyroxin at physiological dose levels (12) and those of cold acclimation in similar systems to the extent permitted by the data at hand.

Comparison of the cold-acclimated rat with the L-thyroxin-treated series was made both with our fraction M_2' (12), a twice washed liver mitochondrial preparation, and also with the Schneider M_w fraction (13). Use of the M_2' preparation enabled simultaneous comparison with the poorly washed M_1 fraction in which P/O ratios were characteristically depressed by either thyroxin (12) or cold acclimation (2). Results reported on cold effects are based on measurements with Long-Evans male rats of terminal weight 300 to 550 gm, exposed individually at a cage temperature of 6°C for 60 to 180 days in a continuously lighted cold room. Techniques and treatment for both these and the thyroxin studies have been described (2, 12).

The variables to be considered here are admittedly a very small part of the total response pattern with which we must be concerned. The following parameters[2] have been studied *in vitro* in liver from surgically thyroidectomized and normal rats as functions of graded doses of L-thyroxin injected daily over a 14-day period:

$$Q_{O_2} = f_1 \text{ (dose)} \quad (1)$$

$$Q_P = f_2 \text{ (dose)} \quad (2)$$

$$\text{Mito TPNHccR} = f_3 \text{ (dose)} \quad (3)$$

$$\text{Micros TPNHccR} = f_4 \text{ (dose)} \quad (4)$$

$$\text{Mito DPNHccR} = f_5 \text{ (dose)} \quad (5)$$

$$\text{Micros DPNHccR} = f_6 \text{ (dose)} \quad (6)$$

$$\text{Total DPN + DPNH} = f_7 \text{ (dose)} \quad (7)$$

Expressing each of the above parameters in terms of activity against log dose, we may obtain a set of equations of similitude which are then capable of being interrelated in many arbitrary ways. To the extent of available data and limitations of analogous behavior these serve as a basis for comparative evaluation of the response pattern of the cold-acclimated rat.

Respiratory Q_{O_2} of the particulates when plotted against log dose of thyroxin shows a straight line relationship of the form:

$$y = c + m\, x_d \quad (8)$$

where x_d is the logarithm of the daily dose in μg/kg body weight. In general, Q_{O_2} of the washed fractions rises markedly with increasing thyroxin dose, while the M_1 system shows either no response or, when the hexokinase-glucose acceptor system is added, becomes negative in slope (table 1).

The Q_{O_2} at a given reference dose is highest in the well-washed M_w mitochondrial fraction and lowest in the poorly washed M_1. While to a considerable extent this reflects increments of extramitochondrial nitrogenous material present in the fractions, the magnitudes and signs of the slope m_1 indicate further that this material is contributing both qualitatively and quantitatively to the response to thyroxin.

[1] This investigation was supported in part by Grants C-3103 and C-3635 from the National Cancer Institute, National Institutes of Health, and by grants from the University of California Cancer Research Coordinating Committee.

[2] Abbreviations used here and elsewhere in the text are as follows:

aKG: alpha ketoglutarate
BOH: beta hydroxybutyrate
ccR: cytochrome *c* reductase expressed in arbitrary units referred to mg N of the sample tested
DPN, DPNH: oxidized and reduced diphosphopyridine nucleotide
intact: donor animals not thyroidectomized
log: logarithm to the base 10
micros: microsomal
mito: mitochondria
Q_{O_2}: microliters of O_2/mg N/hr.
Q_P: micromoles inorganic phosphate exchanged or fixed per mg N per hr.
thyrx: thyroidectomized

TABLE 1. *Numerical Values of Constants* c *and* m *of equation (8)**

Group	c†	m_1
M_w (thyrx)	1022	581
M_w (intact)	1306	204
M_2' (thyrx)	1055	377
M_2' (intact)	828	279
M_1 (thyrx)	621	−85
M_1 (intact)	~440	−33

* Where Y_1 for various liver fractions is the Q_{O_2} corrected for grams body mass (W) and expressed in (μl O_2/mg N/hr) ($W^{0.3}$). † Intercept of *equation* (8) representing ($Q_{O_2}W^{0.3}$) at x_d = 1 μg thyroxin/kg/day (14 days).

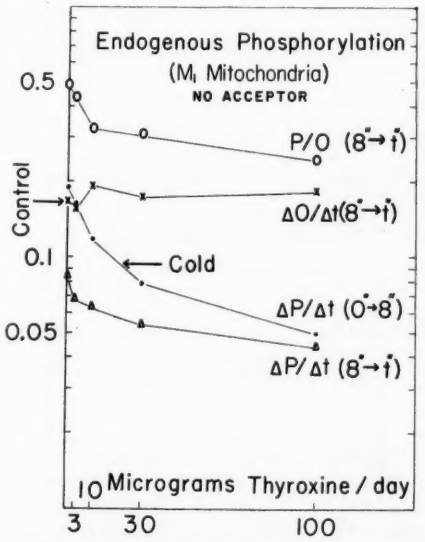


FIG. 1. Endogenous phosphorylation and O_2 consumption in M_1 preparation as function of thyroxine dose. ●: rate of P uptake (μatoms P/mg N/min) during period 0–8 min. △: rate of P uptake during period 8–23 min. ×: rate of O_2 uptake (μatoms O/mg N/min) during period 8–23 min. ○: P/O ratio calculated from △/×. *Arrows* indicate points of equivalent effect in M_1 from cold-acclimated rats.

Oxidative phosphorylation appears essentially unaffected by thyroxin in fractions M_2' and M_w but declines with dose in the M_1 fraction (12). The cold-acclimated rats show similar effects, and these are denoted in reference to the L-thyroxin dose scale in figures 1 and 2, where the cold effect would appear roughly equivalent to thyroxin effects at the 10–30 μg/rat/day dose level, or some 30–100 μg thyroxin/kg body wt/day for these animals.

The 'endogenous phosphorylation' illustrated in figure 1 is that fixation of inorganic phosphate which occurs in the absence of the hexokinase-glucose acceptor system. It is easily detected in the M_1 system, is very low in the M_2', and is essentially zero in the M_w.

The significance of the endogenous phosphorylation is here twofold: *a*) it indicates that the M_1 fraction contains endogenous material capable of fixing phosphate (in a form not hydrolyzed by 0.4 N H_2SO_4 at room temperature), and *b*) it is an intrinsic system which shows sensitivity to such factors as cold acclimation and thyroxin treatment comparable to that obtained with the addition of the exogenous trapping system.

When the hexokinase-glucose acceptor is added to the washed liver mitochondrial fractions of normal rats, the respiration is ordinarily enhanced more than when added to a similar system from a thyroxin-treated rat. The use of this 'acceptor effect' in connection with oxidative phosphorylation derives largely from the observations by Lardy and Wellman (14) and later of Hoch and Lipmann (7) who noted that in 'mildly thyrotoxic' rats the addition of the hexokinase-glucose trapping system to mitochondrial preparations may accelerate respiration without inducing measurable changes in the P/O ratios. These authors took this response to be indicative of a 'loosening' of the normal coupling of respiration to phosphorylation.

As our current studies have demonstrated (12), an acceptor effect is manifest in all of the mitochondrial preparations used; however, it is present in the classical sense only in the washed fractions (M_w and M_2'), while in the M_1 addition of the acceptor inhibits respiration. The relative effect on respiration taken as the ratio (Q_{O_2} + acceptor/Q_{O_2} − acceptor) (fig. 2; cf. table 1 in (17)) is dependent upon the dose in all fractions, and as the M_w and M_2' become less stimulated at higher thyroxin dosages, the M_1 becomes more inhibited. As the slopes of the ratios for the M_w and M_2' against dose are somewhat more negative than that of M_1, the regressions tend to converge; a practical consequence thereof is the extrapolation that the acceptor would also inhibit respiration in M_2' and M_w were the dosages (on the 14-day schedule used here) to be increased to 20,000 μg/kg/day. Since for a 100-gm rat this would amount to a total dose of only 2 mg L-thyroxin per day, it appears not at all improbable that a number of dose regimens which have been employed in various laboratories, either by injection or with feeding, may well be in excess of this level. Under such conditions one might consistently observe depression of respiration upon addition of the trap and either depressed oxidative phosphorylation, as occurs in M_1 fraction, or not, depending on extent of washing of the fraction.

The cold-acclimated rats clearly show (fig. 2) a less pronounced acceptor response than do their controls, irrespective of the fraction used. This for the liver therefore becomes a common parameter of the subcellular response pattern, whatever the causal interpretation placed upon it. It is also evident that this response may or may not be assocated with a measurable change in P/O ratio.

There are several factors which appear to modify the position of the acceptor ratio in respect to apparent thyroxin dose equivalence (as indicated by position on the *x*-axis of the figure). Thus on the lower curve (M_1) the ratios for beta hydroxybutyrate are respectively higher than those with alpha ketoglutarate. The addition of DPN and cytochrome *c* to the medium has the effect

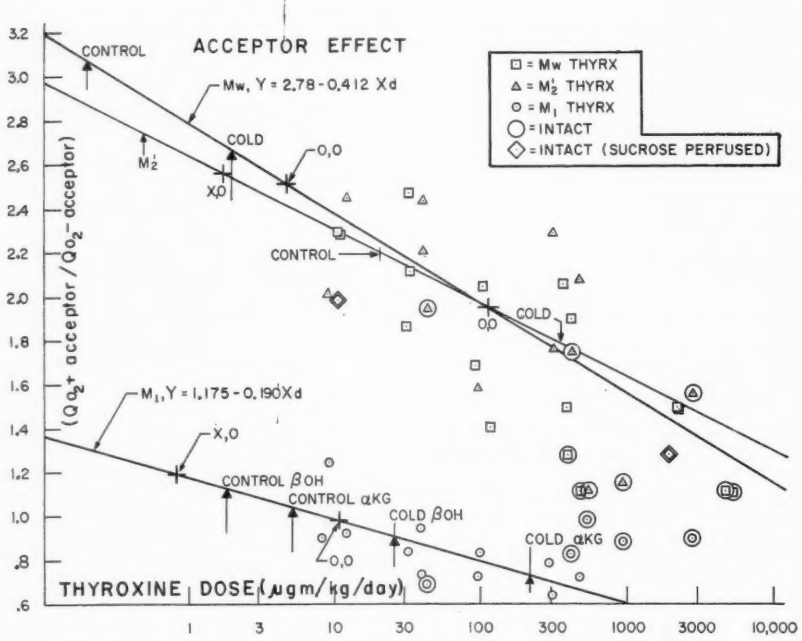


FIG. 2. Ratio of respiration of respective fractions in presence to that in absence of hexokinase-glucose acceptor system vs. logarithm of thyroxine dose rate.

(not illustrated) of raising the respiration of the no-acceptor system, but equally so in both control and cold-acclimated animals. The significance of thyroxin dose equivalence on these curves obviously must be interpreted with caution. The points indicated by arrows or crosses were so placed by computation of X for the various experimental values of Y substituted into the respective regression equations. The regression lines represent only the values for thyroidectomized, thyroxin–treated rats; the points so obtained for the untreated thyroidectomized and intact control rats appear fairly consistent with expectancy as to the thyroxin output.

As initially reported by von Raaflaub (15), optical densities (O.D./mg N at 520 mμ) of suitably diluted mitochondrial suspensions exhibit characteristic changes both initially and during incubation in various media. In this respect the unwashed M_1 fraction from either cold-acclimated or normal animals was shown to be completely protected from significant changes in optical density during incubation in sucrose but to decrease at varying rates when in the presence of substrate (BOH) in a KCl-sucrose phosphate buffered medium (2). More recently (12) extensive trials with freshly isolated M_w particles in tris-sucrose, pH 7.4, have demonstrated that the initial optical density in this instance decreases with dose in thyroxine-treated, thyroidectomized animals. The same fraction from 60-day cold-acclimated animals, however, shows only a slight decrement over controls in initial optical density which then decreases with incubation time at 30°C at a rate indistinguishable from that of the controls. As the initial optical density was higher than that of the thyroidectomized, untreated animals, no assignment to the thyroxine dose scale could

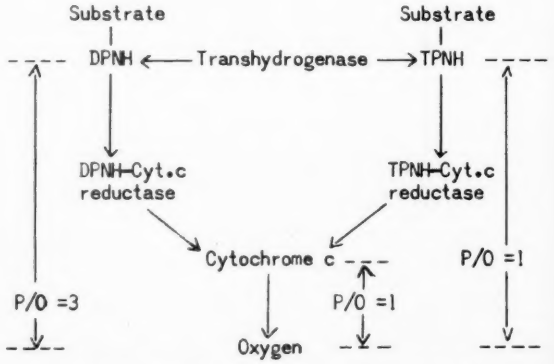


FIG. 3. Diagram illustrating principal features of a pathway whereby increased thermogenesis might result from changes involving a shift from DPNH– to TPNH–dependent pathways and a decrease in net phosphorylative efficiency: *a*) TPNH-cytochrome *c* reductase is doubled in hyperthyroid animals. *b*) Transhydrogenase shown to be inhibited *in vitro* by thyroxin. *c*) The TPN-dependent glucose-6-PO_4 and 6-phosphogluconate dehydrogenases are greatly increased in hyperthyroid rats.

be made; the quesion as to significance of this behavior is left open.

The role of extramitochondrial cytoplasmic factors in the regulation of electron transport and oxidative phosphorylation has continued to present perplexing problems. To test the implications of theory and observations associating cold thermogenesis with depressed oxidative phosphorylation (1, 2), we early undertook to assay changes in the components of the TPNH-DPNH shunt mechanism (see fig. 3). While initial results were not encouraging, it was recognized that at least the

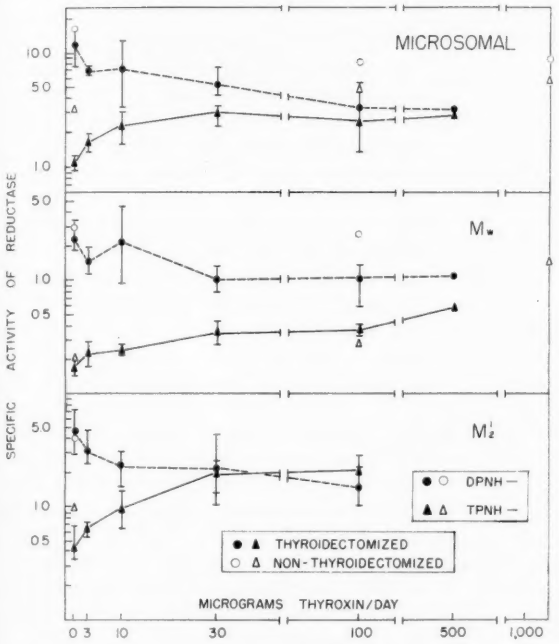


FIG. 4. Activities of DPNH– and TPNH–cytochrome *c* reductases vs. thyroxine dose rate. *Vertical bars* indicate range for M_2' (n = 5), M_w (n = 3), and microsomal fraction of M_w preparation (n = 3).

TPNH-dependent pathways were probably as importantly concerned with extra- as with intramitochondrial processes. Thus attention was given to the subcellular distribution patterns of the TPNH-DPNH-cytochrome *c* reductases in liver of thyroxin-treated, normal and thyroidectomized rats (12), and the comparison of these with cold-acclimated rats. In this work we have confirmed the earlier finding (16) that TPNH-cytochrome *c* reductase activity of the microsomal fraction of liver is increased by thyroxin treatment and have also shown this to be true of washed mitochondria from thyroidectomized and normal rats given physiologic doses of thyroxin. It was further demonstrated that within the physiological dose range the extent of this increase was dose dependent and that it was coincident with a systematic decrease in the measured activity of DPNH-cytochrome *c* reductase in the same fractions (fig). 4. Concurrently the total DPN-DPNH content of the M_w mitochondrial fraction also decreased with dose.

The changes of TPNHccR and of total DPN + DPNH can be fairly approximated by straight line regressions of activities as functions of logarithm of the dose rate; however, similar treatment of the DPNHccR must ignore the rather large initial decrement induced by small doses of the hormone. It is therefore more faithfully represented by a straight line when placed on a log-log plot; however, for the doses larger than 10 μg/kg body weight the regression on log dose is sufficient for descriptive comparisons, and so is used here (table 2).

TABLE 2. *Regression of DPNH-Cytochrome* c *Reductase* (Y_5 *and* Y_6) *and Total DPN + DPNH* (Y_7)*

Y	c	m
(thyrx) M_w Mito, Y_5	1.437	−0.149
(thyrx) M_w Micros, Y_6	8.157	−1.689
(thyrx) M_w Mito, Y_7	14.41	−2.422

Interrelations

$Y_6 = 1.8 + 5.1\ Y_5$†
$Y_5 = 0.55 + 0.06\ Y_7$
Q_{O_2} (intact) M_w Mito, $Y_{1i} = 474 - 42\ Y_5$
Q_{O_2} (thyrx) M_w Mito, $Y_{1th} = 546 - 126\ Y_5$

* As functions of log dose (x_d); equation of form $Y = c + mx_d$.
† Y_5 = (intact + thyrx M_w micros).

Principal features of the response of the DPNccR to thyroxin are: *a*) in the thyroidectomized animals its extreme lability to the smallest dose levels of thyroxin, the lowest dose used (about 10 μg/kg/day) being sufficient to reduce the level by 25%; *b*) the apparent refractoriness to thyroxin of the intact animals relative to the thyrx group; *c*) a strongly negative slope of Q_{O_2} on DPNHccR, which is significantly steeper in the thyrx-treated than in the intact-treated and thyrx-untreated groups (fig. 5). In general agreement with assays by others (17), DPNHccR remains some five times more concentrated in the microsomal than in the mitochondrial M_w fraction.

The total DPN + DPNH concentration of the M_w fraction shows a high sensitivity to thyroxin at all dose levels. In the combined regression of mitochondrial DPNccR on total DPN, the variants exhibit a significant correlation within the thyrx-treated group; however, it also appears that the cold-acclimated animals fall into the same distribution as do intact or nontreated thyrx animals (fig. 6), all of which tend to remain relatively higher in respect to DPNHccR for a given DPN level.

Calculations from regressions (in table 3) of TPNHccR on log dose show that at a dose of 10 μg/kg/day the M_w mitochondrial fraction exhibits a concentration of the reductase of about one-third that found in the M_2' fraction. It appears reasonable to ascribe this difference to the inclusion of microsomal material within the M_2', which on this basis could amount to nearly 70% dilution of the mitochondria in this fraction with microsomal material.

Effects of this dilution should be manifest in a lowered Q_{O_2}, whence one may examine regressions of the latter on TPNHccR (table 4). In these the value of Q_{O_2} at a fixed enzyme level should give indication of relative dilution if no intrinsic effect of TPNHccR on Q_{O_2} obtains. From table 5, the ratio of Q_{O_2} values of M_1/M_w and M_2'/M_w are respectively 21.6% and 48.4% of the M_w value; whence in the M_1 and M_2', microsomal material could be diluting the respective fractions by factors of the order of 5 and 2 times that present in the M_w.

Values of TPNHccR have now been obtained on two series of livers from cold-acclimated rats with no significant differences referable to cold appearing in either.

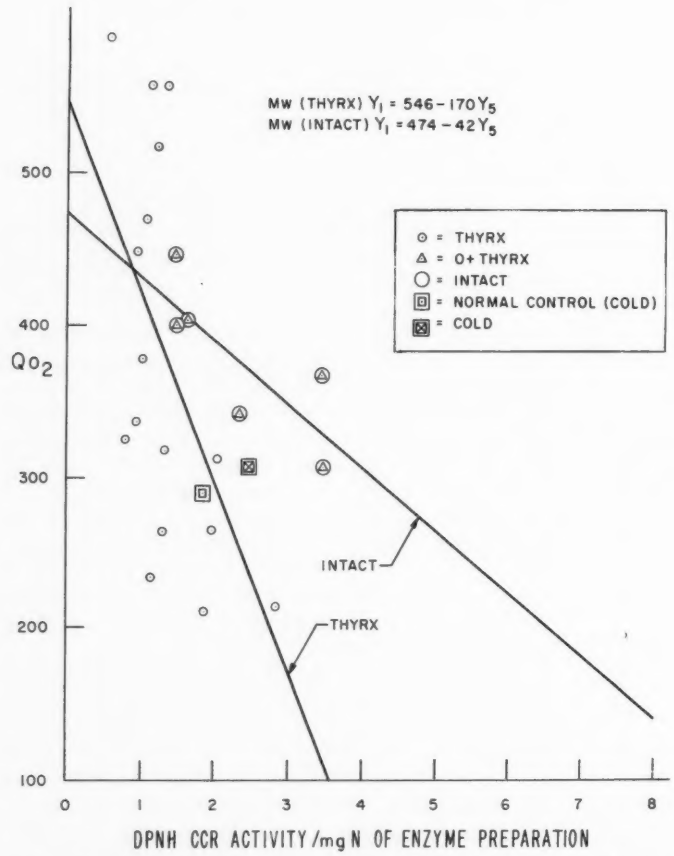


FIG. 5. Q_{O_2} (μl O_2/mg N/hr) vs. activity of DPNH-cytochrome *c* reductase in washed liver mitochondria from variously treated intact and thyroidectomized rats.

In the most recent series, on M_w fraction, cold and controls give respectively 0.220 and 0.215 units/mg N, which values fall well within the scatter of the thyroxin thyrx series. Substituting for Y_3 in table 3 gives the corresponding X_d values of 14.9 and 13.7 μg thyroxin/kg/day.

In the earlier series with M_1 fraction from cold-acclimated animals the regression of Q_{O_2} on TPNHccR for the controls was nearly identical to that obtained for the Q_{O_2} of M_1 vs. the TPNHccR of the M_2' fraction as noted in table 4; for the corresponding cold group, however, the slope of this regression was essentially zero. From the latter regression also it is most evident that Q_{O_2} is significantly depressed below the control value for M_1. Since microsomal dilution factors are here largely nullified, one must presume in this instance at least that Q_{O_2} is essentially independent of the level of TPNHccR of the fraction. As a similar conclusion applies substantially to Q_P, it must also extend to the ratio, P/O, which unlike that of the M_w and M_2' is significantly depressed in the M_1 both in cold and as a function of thyroxin dose.

From the limited sampling of five cold-acclimated rats, the DPNHccR levels were unexpectedly found to be significantly higher than those of the age controls for this series; however, as both fell within the range of the intact and untreated thyrx weight controls, the differences remain of dubious significance. The ratios of M_w DPNHccR/TPNHccR, in cold and control groups respectively, were 11.2 and 9.1, again not significantly different, and the same was true of the total DPN + DPNH of the M_w of this series which ranged around 20 μg DPN/mg N with a suggestion of being lower in the cold group. Though further measurements are needed, the present estimates taken together with the pattern of response to thyroxin appear wholly at variance with the implications of the DPN-TPNH shunt hypothesis as summarized in figure 3. Whence the issue of cellular thermogenesis by this route must remain in the limbo of uncertainty.

The concurrent decreases in total DPN-DPNH and in the DPNHccR in association with the rising level of TPNHccR suggest that the former are giving way to the latter in a manner determined quantitatively by the level of the thyroxine dose. From the data it appears that while TPNHccR reaches an asymptotic activity with the higher dosages, DPNHccR continues to decrease as a straight line function of log dose. This suggests that the level of TPNHccR may be itself limited by the rate constants of its conversion either through DPNHccR or available DPN levels or both. While quantitatively the DPNHccR is many times more concentrated than is the TPNHccR, the steady-state turnover of the TPNH may be quite rapid under these enhanced metabolic conditions. Whence a continuing drain on the DPNH pool could be involved.

A second point to consider is the extent to which synthesis of the DPN may be impaired by the treatment. The striking sensitivity of both DPN and the reductase to low levels of thyroxin suggests that the latter may invoke strong competition for the essential ingredients of DPN synthesis. Conceivably availability of ATP may become a critical factor, since both coenzyme *A* as well as DPN depend heavily upon it for synthesis, and even the TPN synthesis also requires an additional ATP. One may note, however, that while DPN levels decrease, CoA and TPNH (at least TPNHccR) rise markedly.

SUMMARY

Comparisons have been drawn between the behavior of liver mitochondria of cold-acclimated rats and

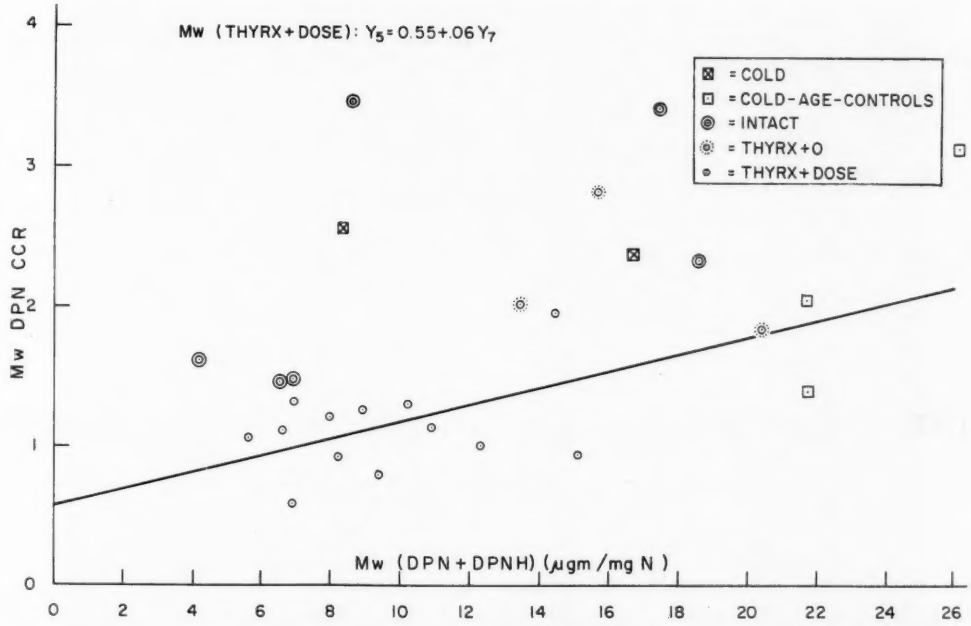


FIG. 6. Plot of activity of DPNH-cytochrome *c* reductase of M_w fraction vs. corresponding levels of total DPN-DPNH concentration. Regression line is based only on points from data for (thyrx + dose).

TABLE 3. *Regressions of TPNH-Cytochrome* c *Reductase of Various Fractions on Log Thyroxin Dose*

		c	*m*	Y at X = 1
Thyrx M_w				
(mito)	Y_3 =	0.0616 + 0.1349 x_d		0.1965
(micros)	Y_4 =	1.4987 + 0.4806 x_d		1.9793
Thyrx M_2'				
(mito)	Y_3' =	−0.3798 + 1.007 x_d		0.6272

TABLE 4. *Regression Equations for* Q_{O_2} (Y_1) *vs. TPNH-Cytochrome* c *Reductase Activity* (Y_3)

		Y_1 at $Y_3 = 0.5$
(Thyrx) M_w	$Y_1 = 167 + 694\ Y_3$	514
(Thyrx) M_2'	$Y_1' = 218 + 61.7\ Y_3$	249
(Thyrx) M_1*	$Y_{1.1} = 120 - 18.1\ Y_3$	111
(Intact) M_1	$Y_{1.1} = 116 - 13.3\ Y_3$	109
(Cold) M_1	$Y_{1.0} = 56 - 3\ Y_3$	58

* Obtained vs. concentration of TPNHccR in corresponding M_2' fraction.

similar fractions obtained from several series of thyroidectomized and intact rats injected daily for 14 days with L-thyroxin in doses within the physiologic as well as the thyrotoxic ranges. Criteria of effect indicate generally analogous behavior of the cold-acclimated to that of thyroxin-treated rats receiving between 10 and 100 μg/kg body w/day; apparently analogous are accelerated respiratory Q_{O_2} and normal P/O ratios of the washed (M_2' and Schneider M_w) mitochondrial fractions and depression of respiration and P/O in unwashed (M_1) fractions, where endogenous phosphorylation was also comparably inhibited; the hexokinase-glucose acceptor system was shown to accelerate Q_{O_2} decreasingly with thyroxine dose but at constant P/O in the washed fractions and concurrently to reduce both Q_{O_2} and P/O in the unwashed M_1; the latter effect was enhanced with increasing dosage. The ratio (Q_{O_2} + acceptor/Q_{O_2} − acceptor), appears to provide a common parameter of target effect, independent of phosphorylative behavior, to the extent that the ratio is always larger for the smaller dose irrespective of extent of washing. The P/O, however, is evidently not correlated with this effect except in the M_1 fraction. Measurements of TPNH- and DPNH-cytochrome *c* reductases and total DPN + DPNH showed comparable subcellular distribution patterns within cold- and thyroxin-treated rats, with the preponderance of the reductases being present in the microsomal fraction. These therefore appear increasingly in the less cleanly washed fractions. The DPNH-cytochrome *c* reductase and total DPN + DPNH appear relatively little affected by cold acclimation, but are sharply depressed in thyroxin-treated, thyroidectomized rats; in the latter TPNH-cytochrome *c* reductase rises with thyroxin to reach a value asymptotic with dose but remains unchanged in cold-acclimated rats. Limiting factors appear to establish the steady-state level of the TPNH-cytochrome *c* reductase possibly at the expense of DPNH and/or DPNH-cytochrome *c* reductase which continues to decrease with dose.

REFERENCES

1. SMITH, R. E. AND A. S. FAIRHURST. *Fed. Proc.*, 17: 598, 1958.
2. SMITH, R. E. AND A. S. FAIRHURST. *Proc. Natl. Acad. Sci. U.S.* 44: 705, 1958.
3. SMITH, R. E. *Fed. Proc.* 17: 1069, 1958.
4. PANAGOS, S. AND R. E. BEYER. *Fed. Proc.* 17: 477, 1958.
5. PANAGOS, S., R. E. BEYER AND E. J. MASORO. *Biochim. et biophys. acta* 29: 204, 1958.
6. MARTIUS, C. AND B. HESS. *Arch. Biochem. Biophys.* 33: 486, 1951.
7. HOGH, F. L. AND F. LIPMANN. *Proc. Natl. Acad. Sci. U.S.* 40: 909, 1954.
8. LARDY, H. In *Brookhaven Symposia in Biology* 7: 90, 1954.
9. SELLERS, E. A. AND S. S. YOU. *Am. J. Physiol.* 163: 81, 1950.
10. LEBLOND, C. P. AND J. GROSS. *Endocrinology* 33: 155, 1943.
11. WOODS, R. AND L. D. CARLSON. *Endocrinology* 59: 323, 1956.
12. FAIRHURST, A. S., J. C. ROBERTS AND R. E. SMITH. *Am. J. Physiol.* 197: 370, 1959.
13. SCHNEIDER, W. C. *J. Biol. Chem.* 176: 259, 1948.
14. LARDY, H. A. AND H. WELLMAN. *J. Biol. Chem.* 195: 215, 1952.
15. VON RAAFLAUB, J. *Helvet. physiol. et pharmacol. acta* 11: 142, 1953.
16. PHILLIPS, A. H. AND R. G. LANGDON. *Biochim. et biophys. acta* 19: 380, 1956.
17. HOGEBOOM, G. H. AND W. C. SCHNEIDER. *J. Natl. Cancer Inst.* 10: 983, 1950.

Submicroscopic analysis of the secretory process in the adrenal medulla[1]

E. D. P. DE ROBERTIS AND D. D. SABATINI

Instituto de Anatomía General y Embriología, Facultad de Ciencias Médicas, Buenos Aires, Argentina

DE ROBERTIS, E. D. P. AND D. D. SABATINI. *Submicroscopic analysis of the secretory process in the adrenal medulla.* Fed. Proc. 19, Suppl. No. 5: 70–78. 1960.—The adrenal medulla of several species was studied with the electron microscope. The special reducing properties of the catecholamines permit visualization of the formation of secretory droplets from the earliest stages and their discharge on the cell surface. The secretory droplet starts in the deep regions of the cytoplasm within vesicles of the Golgi complex, where the catechol material increases in amount and density; the droplets then move toward the periphery and become attached to the surface membrane. Stimulation of the splanchnic nerve induces the excretion of the catechol material as evidenced by the emptying of the membranes which surround the secretion droplets. The possible mechanism involved in the formation, movement and discharge of the catecholamines is discussed and compared with other neurohumoral secretions.

THE ADRENAL MEDULLA is a gland of neural origin directly connected to the nervous system by way of the splanchnic nerve. The main cellular elements of this tissue represent modified postganglionic neurones which exhibit neurosecretion in response to nervous stimulation. The synapse between the splanchnic nerve and the adrenomedullary cell is mediated by acetylcholine (1). This anatomical relationship makes this tissue especially adapted to respond quickly to situations of environmental stress such as cold or to metabolic stresses such as changes in homeostatic equilibrium resulting from hypoglycemia, hypotension, etc.

In the course of the years, several products of the catechol series, including adrenaline (2–4), noradrenaline (5), dopa (6), dopamine (7) and isopropylnoradrenaline (8) have been demonstrated in adrenomedullary tissue. Of these, only adrenaline and noradrenaline (NA) are detectable in the effluent blood in significant amounts and thus are considered to be the products of secretion.

From the histological and histochemical viewpoint, the prevalent idea is that there are two types of cells involved in either adrenaline or NA secretion. These two types of cells can be demonstrated by the iodate reaction of Hillarp and Hökfelt (9) or the fluorescent test of Eränko (10). Different physiological experiments on the discharge of catecholamines (11, 12) give support to the idea that these cellular types are permanent and do not represent different stages of a single secretory cycle.

It is generally considered that certain stimuli elicit specifically one or the other type of secretion. However, in the case of the action of cold there are species differences and the action has not yet been definitely clarified. Thus, Allen (12) found that cold liberates noradrenaline from the medulla of the mouse while Des Marais and Dugal (13) and Fisher *et al.* (14) observed an accumulation of noradrenaline in the medulla of the rat.

The problem of cell types has been followed at the biochemical level and both adrenaline and NA were found in a granular fraction which was at first isolated together with mitochondria (15, 16). More recently this granular fraction has been isolated in a more pure

[1] Work supported by grants of the Argentine National Research Council and the Rockefeller Foundation of New York.

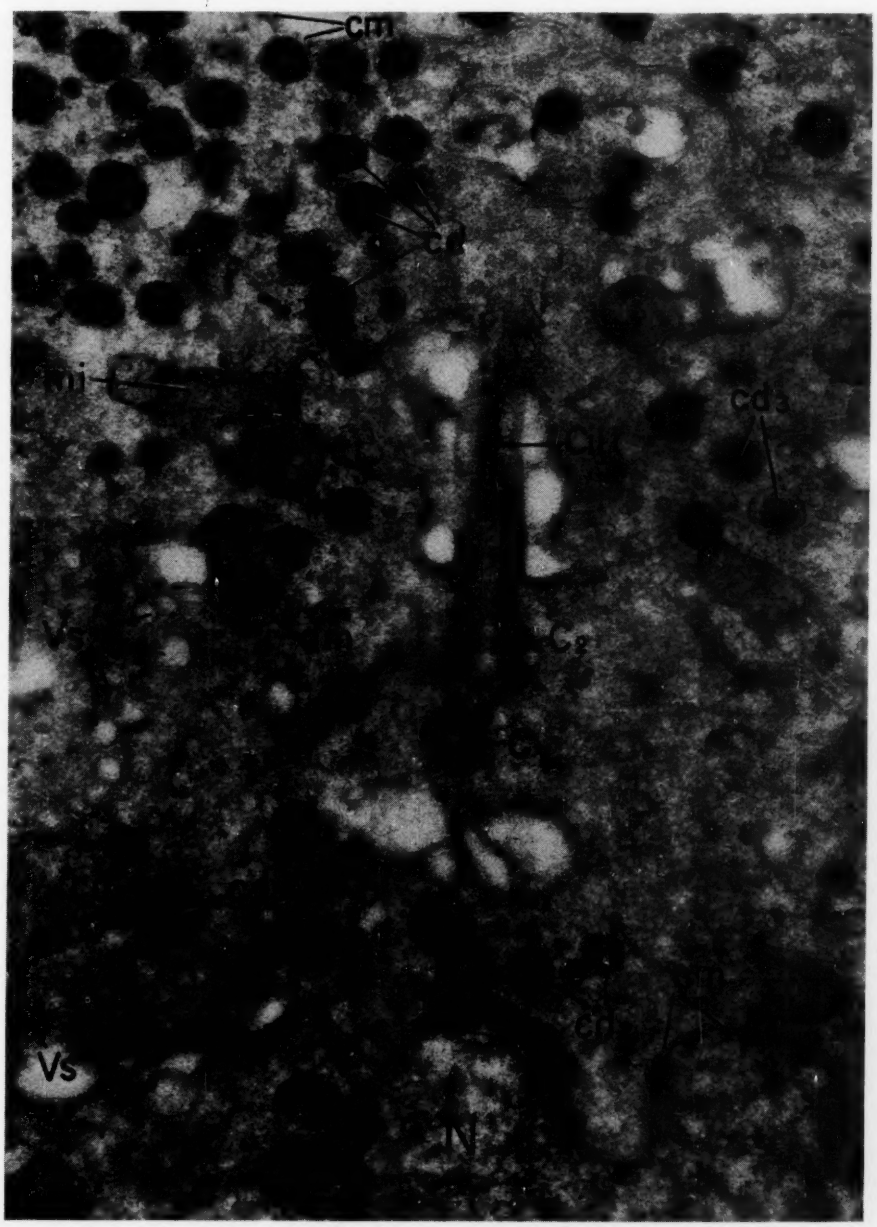


FIG. 1. Electron micrograph of a chromaffin cell from the adrenal gland of the hamster. At the bottom the nucleus (*Nc*) with the folded nuclear membrane (*nm*) can be seen. The supranuclear portion of the cytoplasm shows the Golgi complex (*G*), two centrioles (C_1, C_2) with a cilium (*Cil*) arising from one of them, several mitochondria (*mi*) and the catechol containing droplets (*cd*). The smaller catechol droplets (cd_1, cd_2) appear in the Golgi zone. Within some small Golgi vesicles (*Vs*) the dense deposit is first observed. As the vesicles enlarge and the content increases (cd_2, cd_3) the clear space under the droplet membrane (*dm*) narrows. Completely formed catechol containing droplets (*cd*) occupy the peripheral part of the cytoplasm near the cell membrane (*cm*). 51,500 ×.

form (17, 18). Another interesting finding is that within these granules the catecholamines are accompanied by an equivalent amount of ATP (19, 20).

In the present report we shall describe some of our observations related to the submicroscopic analysis of the formation and excretion of catechol-containing droplets in the adrenal cells. This type of work can be very favorably carried out at the level of the electron microscope since both adrenaline and NA have intense reducing properties and react very rapidly with the OsO_4 used in the fixation. As early as 1902, Plenick observed the immediate reaction of OsO_4 in the adrenal

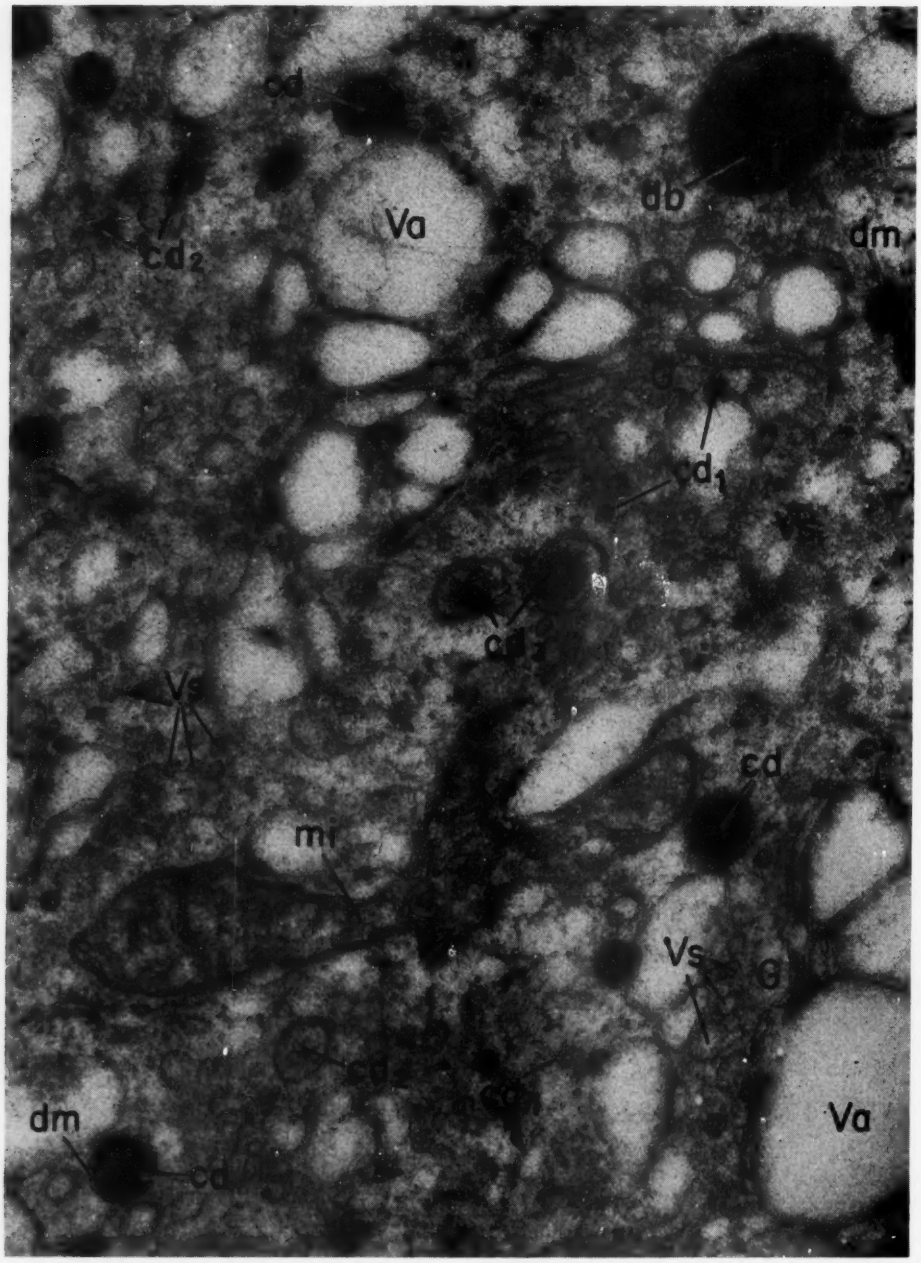


FIG. 2. Deep region of the cytoplasm of an adrenomedullar cell of the hamster. The Golgi complexes (*G*) are conspicuous and consist of flattened sacs, large vacuoles (*Va*) and abundant vesicles (*Vs*). Intermediate stages (cd_2, cd_3) in the formation of the secretory granules are clearly seen. 62,000 ×.

tissue and since then this treatment has been widely used for the localization of catechols in the adrenal medulla (21). For this reason the formation and excretion of the catechols can be followed at the level of resolution given by the electron microscope.

SUBMICROSCOPIC MORPHOLOGY OF THE CHROMAFFIN CELL

Some of the submicroscopic characteristics of the chromaffin cells are shown in figures 1–4 corresponding to adrenal glands of the hamster and rabbit. The nucleus shows deep invaginations of the nuclear membrane

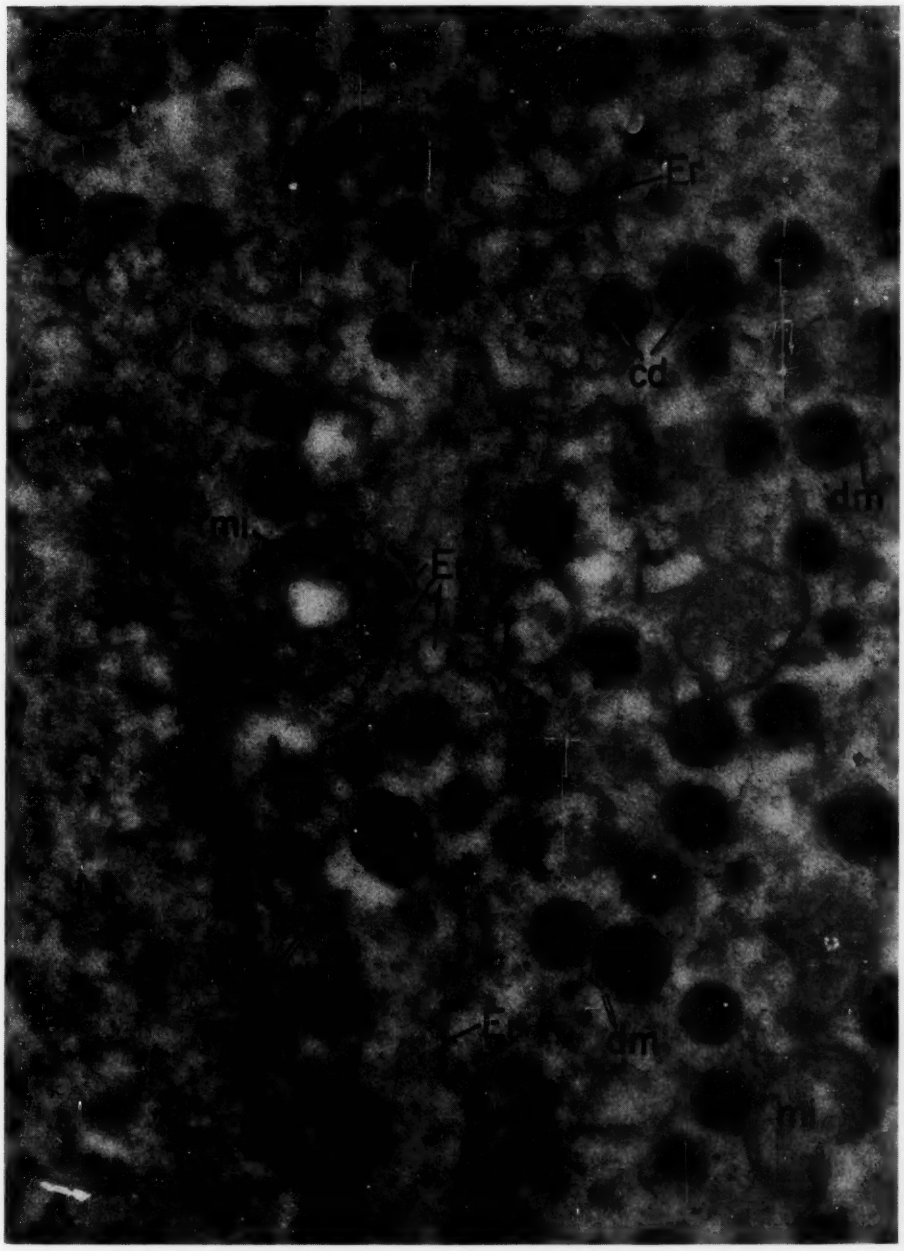


FIG. 3. Part of an adrenomedullar cell of the hamster. The dense content of the droplets (*cd*) is quite homogeneous in this animal, and the droplet membrane (*dm*) is observed in nearly all granules. A perinuclear cisterna is enclosed by the 'double nuclear membrane' (*nm*). A vesicular body (*Vb*), *RNP* granules and cisternae of the endoplasmic reticulum and mitochondria (*mi*) may be seen. 51,500 ×.

(fig. 1). The flattened cisternae of the endoplasmic reticulum, studded on the outer surface with RNP granules, are packed in a parallel array in a localized region of the cytoplasm. Dispersed within the cytoplasm (see fig. 1) there are mitochondria (*mi*) and secretion granules (*cd*). Near the nucleus membrane (*nm*) a localized Golgi complex (*G*) can be found and we have occasionally observed two centrioles (C_1, C_2) and even a cilium (*Cil*) arising from one of them.

The most conspicuous component of the adrenal cell

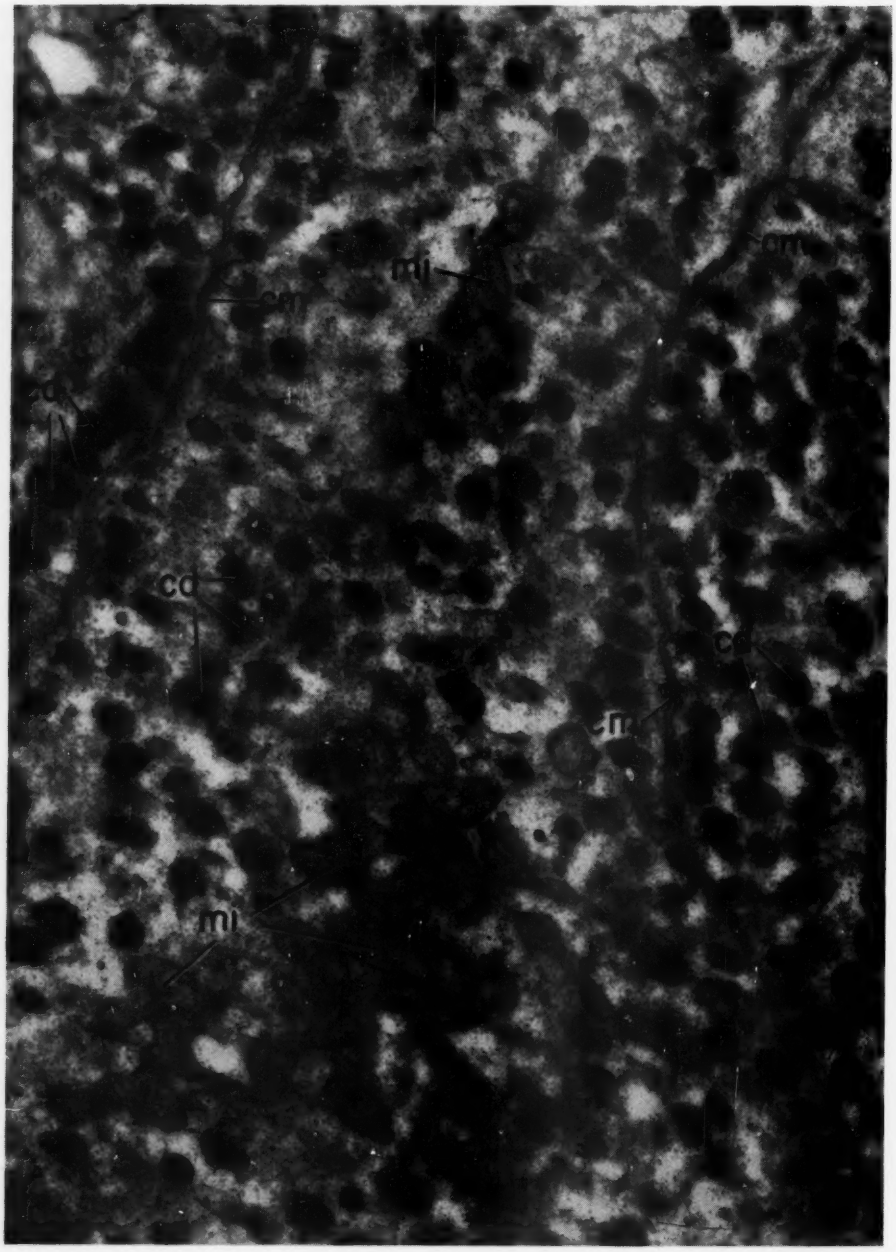


FIG. 4. General view of the cytoplasm of three chromaffin cells from the adrenal gland of a normal rabbit. The catechol droplets are numerous and some of them are lying in the close vicinity of the cell membrane (*cm*). 41,000 ×.

is represented by the catechol containing droplets (*cd*) which can be clearly differentiated from the mitochondria as was demonstrated by Sjöstrand and Wetzstein (22) and De Robertis and Vaz Ferreira (23) in different species. In the rabbit (fig. 4) these droplets have a diameter of about 160 mμ but smaller ones of 40 mμ or less can be seen in the deeper region of the cytoplasm. Between the small droplets and the larger ones there are all intermediary stages (figs. 1 and 2). All these droplets have a limiting membrane (*dm*) which is separated from the dense content by a clear space 100–200 Å in width. The dense content of the droplet is quite homogeneous in the hamster (fig. 3) but much less in the rabbit (fig. 4) and in the rat, in which case it is formed of dense irregular granules. In the toad the electron density of the granules is lower but

FIG. 5. Electron micrograph of adrenomedullary cells from the rabbit after stimulation of the splanchnic nerve. The cytoplasm is nearly free of catechol containing droplets (*cd*), and those which remain are at the periphery of the cell. Several empty droplets (*ed*) can be observed attached to the cell membrane (marked with *arrows*). 41,000 ×.

they are larger than in the other species studied. In the adrenal medulla there are numerous preganglionic nerve fibers coming from the homolateral splanchnic nerve and making a terminal contact with the chromaffin cells. This type of junction is generally considered to be a real synapsis (fig. 6*A*) containing the typical synaptic vesicles (*sv*) (24). It had been seen that the content in synaptic vesicles of the nerve endings varies with the frequency of the stimulus applied to the splanchnic nerve and that this is maximum at frequencies producing the most intense liberation of catecholamines (fig. 7*B*) (24).

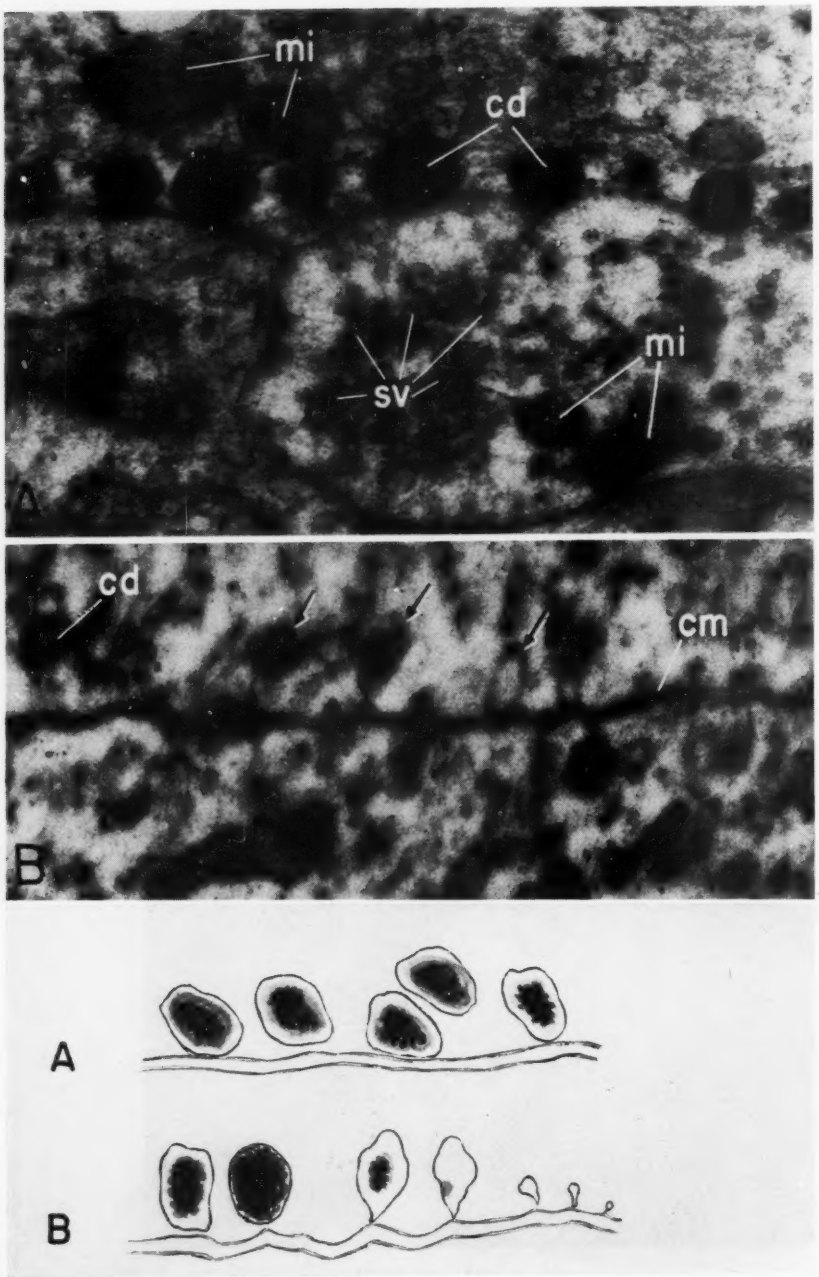


FIG. 6. *A:* Synapsis in the adrenal medulla of the hamster, See the synaptic vesicles (*sv*) and mitochondria (*mi*) within the nerve ending. The catechol droplets (*cd*) of the chromaffin cell are lying in contact with the cell membrane (*cm*). 63,5000 ×. *B:* Excretion of the secretory material in a cell from the adrenal medulla of the rabbit after stimulation of the splanchnic nerve. *Arrows* indicate catechol-containing droplets attached to the cell membrane (*cm*). The process leads to the complete excretion of the catechol and the disappearance of the empty membranes. 50,000 ×.

FORMATION OF THE CATECHOL CONTAINING DROPLETS

The study of the deeper region of the chromaffin cell and particularly of the zone of the Golgi complex has permitted us to follow the formation of the first catechol droplets. As is shown in figures 1, 2 and 7, in the Golgi complex there are flattened sacs, large vacuoles (*Va*) and small and abundant vesicles (*Vs*). The first stage (cd_1) in the formation of the secretion is indicated by the presence of dense deposits within some of the small Golgi vesicles. From the initial stages (cd_2, cd_3 in fig. 2) there is a clear space between the dense material and the membrane of the vesicle. The space becomes more reduced as the size of the vesicle increases and the amount and density of the content becomes larger. In the region of the Golgi complex all stages of development of the catechol droplet can be found. With the increase in the elaboration and storage of the secretory material the droplets become larger and denser (cd_2, cd_3, *cd*) reaching

finally the diameter indicated above. At the same time the material is moved toward the peripheral region of the cytoplasm (fig. 7) and frequently accumulates in the vicinity of the surface membrane (*cm* in figs. 1, 4 and 7).

EXCRETION OF THE CATECHOL-CONTAINING DROPLETS

De Robertis and Vaz Ferreira (23) studied the excretion of catechol droplets using electrical stimuli of the splanchnic nerve in the rabbit. With rectangular supramaximal pulses of a frequency of 40 to 100 pulses per second they found considerable changes which in 10 minutes may lead, in some cells, to a complete liberation of the catechols. This type of stimulus was chosen because Rapela and Covián (25) had previously demonstrated a maximum liberation of catechol in the efferent blood with that treatment.

After stimulation, the content of the droplets shows a decrease in density (fig. 5). The outer membrane of the droplets is now very conspicuous and tends to become irregularly folded (fig. 6*B*). The clear space below the membrane increases considerably while the content of the droplet decreases and very frequently there are empty droplets in the cytoplasm (*ed* in figs. 5 and 7). The study of favorable sections shows that the catechol droplets become attached to the cell membrane (fig. 5, *arrows*, and figs. 6*B* and 2). In the first stage there seems to be an increase in the size of the droplet with a reduction in electron density. At this stage the clear space is no longer apparent. Later, excretion takes place, probably through the attached portion of the membrane and the droplet becomes evacuated and may leave a completely empty membrane (*ed* in figs. 5, 6*B* and 7).

NATURE OF THE SECRETORY DROPLETS

Since the finding of Blaschko and Welch (15) that the catecholamines are found in a granular fraction, several opinions have been postulated on the nature of these granules.

They were first considered comparable to mitochondria because they were conjointly isolated in the same fraction (26). This presumption was supported by the behavior of the granules in hypotonic solutions, detergents and at different temperatures and pH. That this concept was erroneous was first demonstrated with the use of the electron microscope by Sjöstrand and Wetzstein (22) and De Robertis and Vaz Ferreira (23), and later also biochemically by Hillarp (17) and Barrnett and Hagen (18) with better techniques of cell fractionation. The special permeability properties of these catechol droplets can be ascribed to the presence of a surface membrane.

However the concept has remained in the literature that the catechol droplets or granules are real cellular organoids. This opinion was first maintained by Hillarp (27), and Carlsson *et al.* (28) have shown that the protein content of the granular fraction is maintained after stimulation of the splanchnic nerve and they suppose that these granules, after liberation of the amines and the ATP, persist as such within the cell.

Our observations on the secretory cycle of the chromaffin cell in the rabbit leads to a different concept. We have seen that the number of droplets increases after sectioning the splanchnic nerve while after nerve stimulation, the number of droplets decreases and can even disappear from the cells leaving some empty membranes. These two facts are better interpreted

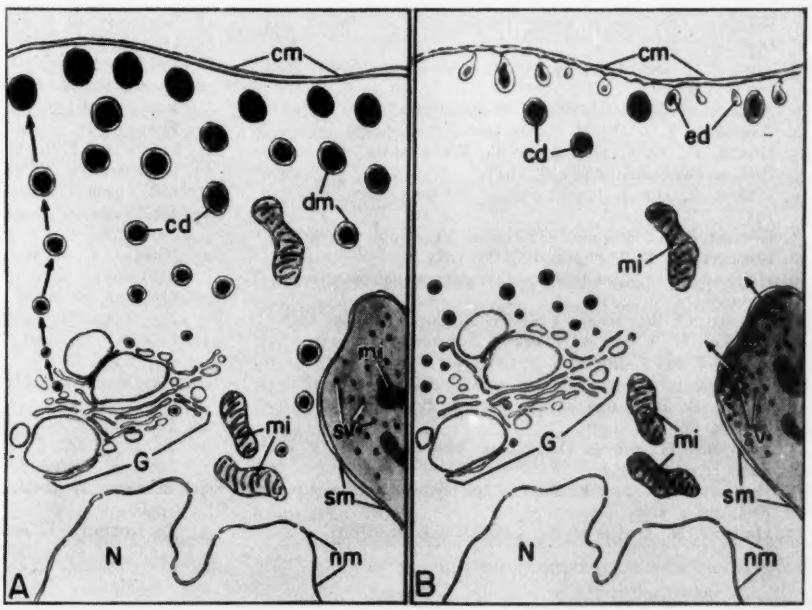


FIG. 7. Diagrammatic interpretation of the mechanism of secretion in the chromaffin cell. *A*. Cell in the resting condition showing the storage of mature catechol droplets in the outer cytoplasm. Near the nucleus within the Golgi complex new secretion is being formed at a slow rate. At the right a portion of a nerve terminal showing the synaptic vesicles (*sv*) and mitochrondria (*mi.*) *B:* Cell after strong electrical stimulation by way of the splanchnic nerve. The catechol droplets (*cd*) have disappeared and the few left are seen in different stages of their excretion into the intracellular cleft. The Golgi region is now forming new droplets at a higher rate. The nerve ending shows an increase of synaptic vesicles with accumulation at 'active points' on the synaptic membrane.

if the catechol droplets are considered as secretory inclusions and not as permanent organoids. The quantity of secretion droplets present at a definite moment is the result of the balance between the process of elaboration and excretion.

CELL TYPES IN ADRENAL MEDULLA

The analysis of the submicroscopic morphology of the chromaffin cell does not yet permit the differentiation of two types of specific cells as can be done with histochemical techniques. We have studied this problem to a certain extent in the hamster since in this species there is a topographic distribution of the cells so that those containing NA are at the periphery (29). We have found that the submicroscopic structure of the cells is very similar in the different regions of the gland.

If the difference between the two cell types resides only in the presence of an enzymatic system (in the adrenaline cells, for the methylation of NA), this negative result could be expected, since it might not have a structural expression at the level shown by the electron microscope. It is interesting that the cells containing NA have, according to Allen *et al* (30), a higher stearase activity. The authors suggest that this might be due to a richer innervation of the cells that secrete noradrenaline. In the hamster we have seen with the electron microscope that synaptic endings are more abundant in certain cells than in others. However no systematic quantitative study of this point has been made so far.

MECHANISM OF SECRETION

The formation of the catechol material within the vesicles of the Golgi region of the cell followed by the increase in size and density of the droplets, the displacement of the droplets toward the surface of the cell and the final excretion at this level, can all be interpreted within the concept proposed by Bennett (31) for the active transport of substances within cells. De Robertis (32) has pointed out that this mechanism is probably active in the synthesis and delivery of different neurohumoral substances such as acetylcholine, catecholamine and the polypeptide-neurohypophysial hormones.

In all these cases the active products are probably formed within a vesicle and then are delivered toward the surface membrane to be liberated instantaneously under the action of the nerve stimulus. The finding that the catechol droplets contain also a high concentration of ATP and that the stimulation of the adrenal gland reduces the ATP content of the tissue (27) tends to indicate that this component is closely related to the catecholamines in the processes of storage and excretion.

De Robertis and Vaz Ferreira (24), have demonstrated that the content of synaptic vesicles increases in the nerve endings of the adrenal medulla with stimulation of a frequency of 100 pulses per second, which has the strongest effect on the liberation of catecholamines. Under the action of this stimulus there is probably an increased liberation and synthesis of acetylcholine in the nerve terminals. However it remains to be explained by which mechanism this acetylcholine released by the terminals exerts its action on the chromaffin cells which will finally produce the excretion of the catecholamine in the intercellular spaces.

REFERENCES

1. Feldberg, W. and B. Minz. *Pflügers Arch. ges. Physiol.* 233: 657, 1933.
2. Abel, J. J. and A. C. Crawford. *Bull. Johns Hopkins Hosp.* 8: 151, 1897.
3. Aldrich, T. B. *Am. J. Physiol.* 5: 457, 1901.
4. Takamine, J. *J. Physiol.* 27: 29, 1901.
5. Holtz, P., K. Gredner and G. Kroneberg. *Arch. exper. Path. u. Pharmakol.* 204: 228, 1947.
6. Werle, E. and J. Juntgen-Sell. *Biochem. Ztschr.* 327: 259, 1955.
7. Goodal, McC. *Acta physiol. scandinav.* 24, Suppl. 85, 1951.
8. Lockett, M. F. *J. Physiol.* 124: 67, 1954.
9. Hillarp, N. A. and B. Hökfelt. *Acta physiol. scandinav.* 30: 55, 1953.
10. Eränko, O. *Acta physiol. scandinav.* 25, Suppl. 89: 22, 1951.
11. Hillarp, N. A. and B. Hökfelt. *Endocrinology* 55: 255, 1954.
12. Allen, J. M. *J. Histochem.* 3: 1, 1955.
13. Des Marais, A. and L. Dugal. *Can. J. Med. Sci.* 29: 90, 1951.
14. Fisher, E., B. Fisher and E. Fedor. *Proc. Soc. Exper. Biol. & Med.* 89: 140, 1955.
15. Blaschko, H. and A. D. Welch. *Arch. exper. Path. u. Pharmakol.* 219: 17, 1953.
16. Hillarp, N. A. and B. Nilson. *Kgl. Fysiograf. Sällskap., Lund Förh.* 23: 4, 1953.
17. Hillarp, N. A. *Acta physiol. scandinav.* 43: 82, 1957.
18. Barrnett, R. J. and P. B. Hagen. *Anat. Rec.* 133: 359, 1959.
19. Hillarp, N. A., B. Högberg and B. Nilson. *Nature, London* 176: 1032, 1955.
20. Falck, B., N. A. Hillarp and B. Högberg. *Acta physiol. scandinav.* 36: 360, 1956.
21. Bennett, H. S. *Am. J. Anat.* 69: 333, 1941.
22. Sjöstrand, F. S. and R. Wetzstein. *Experientia* 12: 196, 1956.
23. De Robertis, E. and A. Vaz Ferreira. *Exp. Cell Res.* 12: 568, 1957.
24. De Robertis, E. and A. Vaz Ferreira. *J. Biophys. & Biochem. Cytol.* 3: 611, 1957.
25. Rapela, C. E. and M. R. Covián. *Rev. Soc. argent. biol.* 30: 157, 1954.
26. Hillarp, N. A., B. Hökfelt and B. Nilson. *Acta anat.* 21: 155, 1954.
27. Carlsson, A. and N. A. Hillarp. *Acta physiol. scandinav.* 37: 235, 1956.
28. Carlsson, A., N. A. Hillarp and B. Hökfelt. *J. Biol. Chem.* 227: 243, 1957.
29. Eränko, O. *Acta endocrinol.* 18: 174, 1955.
30. Allen, J. M., O. Eränko and R. L. Hunter. *Am. J. Anat.* 102: 93, 1958.
31. Bennett, H. S. *J. Biophys. & Biochem. Cytol.* 2, Suppl.: 99, 1956.
32. De Robertis, E. *Intern. Rev. Cytol.* 8: 61, 1959.

Exposure to cold and catecholamines

U. S. VON EULER

Fysiologiska Institutionen, Karolinska Institutet, Stockholm, Sweden

VON EULER, U. S. *Exposure to cold and catecholamines.* Fed. Proc. 19, Suppl. No. 5: 79–81. 1960.—Estimations of the chromaffin reaction in the adrenal gland of animals exposed to cold have shown that when the cold stress was moderate and the animals remained in a good state over a prolonged period, a more or less normal picture was observed in the adrenal medulla. Likewise, in cold-adapted animals the catecholamine content in the gland may be normal or even increased. From these observations it is hard to draw conclusions as to the actual release. On the other hand acute cooling, accompanied by a fall of body temperature of several degrees C, is followed by a definite increase in the release of adrenaline and also by its depletion in adrenal glands. The importance of following continuously the catecholamine production over prolonged periods of cold stress and adaptation by measuring the output in urine is emphasized.

A NUMBER OF STUDIES regarding the cathecholamine content of the adrenals, and the production and release of catecholamines in response to cold stress and in the acclimation processes to cold have been performed since the pioneer studies by Cannon and his associates.

The activation of the adrenergic vasomotor nerves to the skin and other regions when the organism is exposed to cold or when the temperature in heat regulating centers falls is clearly shown by the extensive studies of Cannon and his co-workers (1, 2) and by Satow (3) and Wada and Fuzii (4). From the observations on the denervated heart in medullectomized animals it appears that catechol hormones from extramedullary sources are liberated in considerable amounts as a result of cold stimuli. The effect of adrenaline and noradrenaline released by cold is mainly due to their vasoconstrictor action and to their stimulating effect on metabolism. Whether or not other catecholamines known to occur in the body normally, such as dopamine, have any effect in this respect is at present not known.

CHROMAFFINITY IN ADRENAL MEDULLA AFTER EXPOSURE TO COLD

Several investigators have studied the chromaffin cells in sections of the adrenal medulla after exposure to cold. Staining sections of the mouse adrenals with osmic vapors, Cramer (5) observed that exposure of mice to wet and cold (+5°C for 1–4 hours), which lowered the body temperature to below 32°C, caused complete exhaustion of the fine granules of the medulla which indicate the presence of adrenaline. On the other hand the adrenal medulla of an animal, which remained well after exposure to cold overnight for 9 consecutive nights and then was killed, presented an almost normal picture similar to that in the 'resting' gland. Cramer remarks that the appearance of a 'resting' gland does not preclude continuous secretion of a moderate degree.

The chromaffin reaction in the adrenals of the rat exposed to 4°C was studied by Vincent (6) who found that the reaction disappeared.

A remarkable diminution of the chromaffin reaction in the rat adrenals was also observed by Kayser (7) when the animals were exposed to +8°C. Similar changes were observed in the golden hamster (*Cricetus auratus*) and also in some cases in *Myoxus glis* and *Myoxus arbor*. At 18°C the chromaffin reaction in all animals was normal. After exposure to cold it took 6 hours for the rat at 20°C to replenish its stores. If the ambient temperature was lowered from 28°C to 8°C no change was observed during 6 hours.

More recently Fisher *et al.* (8) have confirmed that rats subjected to hypothermic levels of cold by immersion in an ice bath at +1°C, with rectal temperatures maintained at 18°–23°C, failed to show any alteration in the chromaffin reaction of the adrenal medulla. Moreover they showed, by using the differential staining method of Hillarp and Hökfelt (9), that no change occurred in the noradrenaline cells.

According to Morin (10) and Schaeffer (11) not only the adrenal cortex shows hypertrophy as a result of prolonged exposure to cold, but also the adrenal medulla.

ADRENALINE SECRETION FROM THE ADRENALS INDUCED BY COLD

The effect of cooling on the adrenaline secretion of the unanaesthetized dog was studied by Wada, Seo and Abe (12). They found that when cooling caused a considerable fall in body temperature there was a marked increase in adrenaline secretion. Thus when the normal dog was immersed in water of 0.5°–1°C for 20–40 minutes and the rectal temperature fell to about 30°C there was always an increased rate of adrenaline secretion. Immediately after withdrawal of the animal from the cold bath into room temperature the secretion reached its peak, on an average 0.3 μg/kg/min. Thereafter the secretion rate diminished but remained high as long as the body temperature was subnormal (about 2 hours).

If superficial cold was applied (immersion in water of 5°–7°C, or placing the animal on a block of ice for ½ hour), causing a fall in body temperature of 0.5°–

1.7°C, no increase in adrenaline secretion rate was detectable. Ingestion of cold water at 5°C in amounts of 1000–1500 ml, causing a small decrease in body temperature, increased the adrenaline secretion slightly, the rate being 0.05–0.2 μg/kg/min., on an average 0.1 μg/kg/min. (13).

These experiments have clearly shown, in the unanesthetized dog with exteriorized adrenal, that the cold stimulus has to be of a relatively strong degree in order to increase adrenaline secretion from the adrenals. On the other hand the rate of secretion may be considerable when the animal is exposed to severe cold and is then accompanied by a definite hyperglycemia and a marked paradoxical pupil reaction (14).

Cooling, causing a fall in body temperature to about 30°C, activates the sympathetic system to such a high extent that the overflow of catecholamines from the nerve endings and other extramedullary sources is sufficient to raise the rate of the denervated heart in the medullectomized dog by 20–30 beats per min. (15). In the cat, Cannon *et al.* (2) found, however, that the cardioacceleration on cooling, caused either by cold air or by cold water introduced into the stomach, was almost completely abolished after exclusion of the adrenal medullary secretion.

Liberation of adrenaline from the adrenal medulla of the adult rat, exposed to cold, has also been observed by Long (16), who used the depletion of ascorbic acid in the adrenals as an indicator.

TABLE 1. *Adrenaline and Noradrenaline Content in Both Adrenals of 140–160-gm Rats Exposed to Cold**

	Exposure *days*	Adr. *μg*	Noradr. *μg*
At 0°C, not adapted:	1	9.9	4.1
	9	18	6.4
	18	15.6	6.9
	24	30.1	15.7
At 0°C, adapted:	33	27.0	15.5
	43	25.7	17.5
	75	30.1	18.7
At 10°C:	4	6.6	1.8
	10	13.3	4.5
	18	17.7	12.3
	24	16.6	11.2

* From Des Marais and Dugal (18).

TABLE 2. *Adrenaline and Noradrenaline in the Hedgehog**

	No. of Animals	Adr. *μg/kg b.wt.*	Noradr. *μg/kg b.wt*
	Awake		
Early summer	5	138	84
Midsummer	6	159	73
Autumn	4	183	30
	Hibernating		
Early winter	2	322	37
Midwinter	9	281	15
Early spring	3	320	78
	Awake		
Spring	2	157	34

* From Suomalainen and Uuspää (21).

ADRENALINE AND NORADRENALINE LEVELS IN PLASMA AND IN ADRENALS FOLLOWING EXPOSURE TO COLD

In a study of the catecholamine level in plasma in man immediately following local exposition to localized cold (cold pressor test, one hand immersed in water of +4°C for 1 minute), Manger *et al.* (17) showed that increased figures occurred only in one instance and was unchanged in eight cases. This is in agreement with the results of the Japanese workers who found that a limited superficial cold stimulus did not increase the adrenaline secretion from the adrenal medulla.

In addition to the previously mentioned studies on histological sections of the adrenal medulla, direct estimations of the content of adrenaline and noradrenaline have also been made in the adrenals from animals exposed to cold.

Des Marais and Dugal (18) have made an extensive study of this kind on rats weighing 140–160 grams. The animals were exposed to temperatures of 0°C for periods up to 75 days and to +10°C for periods up to 24 days. Their results showed low figures for both adrenaline and noradrenaline after exposure for 1 day at 0°C and 4 days at +10°C. Thus the adrenaline figure was 9.9 μg in both adrenals after 1-day exposure to 0°C. Using the mean body weight figure of 150 grams, the value was only 66 μg/kg/b. w. as against the normal figures in the material of Hökfelt (19) which were 148 μg/kg for females and 196 μg/kg for males. After 9 days the corresponding adrenaline figures were 120 μg/kg and after 24 days 200 μg/kg which is comparable to the normal content found by Hökfelt. Between 24 and 75 days, when the animals were fully adapted, there was no further change in the adrenaline content (table 1).

The noradrenaline figures showed a steady increase from about 27 μg/kg which was close to that found by Hökfelt in normal rats (31 μg/kg in males and 28 μg/kg in females) to 105 μg/kg after 24 days and 125 μg/kg after 75 days. Thus the noradrenaline content showed a strong increase during prolonged exposure to cold. In the animals exposed to a temperature of +10°C the adrenaline figures increased from the low figure of 44 μg/kg after 4 days to 110 μg/kg after 24 days and the noradrenaline figures from 12 μg/kg after 4 days to 75 μg/kg after 24 days.

These results indicate that after a primary depletion of adrenaline, and possibly noradrenaline, the content of the amines in the gland increases gradually over a period of 24 days to figures which are higher than normal in both groups of animals for noradrenaline while the adrenaline figures were not significantly changed.

In view of the findings of Hsieh and Carlson (20) that noradrenaline has little effect in warm-adapted rats but causes marked calorigenic response in cold-adapted rats this finding is of interest. Further experiments are needed to determine whether the increased content of

noradrenaline in the cold-adapted rats is accompanied by an increased secretion of this amine.

ADRENALINE AND NORADRENALINE IN THE ADRENAL GLAND DURING HIBERNATION

The catecholamine content of the suprarenals has been measured in the hedgehog during summer activity and during hibernation by Suomalainen and Uuspää (21). The amounts of adrenaline and noradrenaline expressed in μg/kg b. wt. is given in table 2.

As seen in the table the adrenaline figures show a definite maximum during the hibernating period and a marked drop in the spring. The noradrenaline figures show no definite trend in this material.

DISCUSSION

From the brief survey of studies regarding the catecholamine formation and release presented here, it is obvious that measurement of the catecholamine production in chronic experiments has not so far been achieved. However, several papers have dealt with the histological picture and the strength of the chromaffin reaction. The actual catecholamine content of the gland has also been measured at various times during acute and prolonged cold exposure. Adrenaline secretion from the adrenals has been measured directly in acute experiments.

The difficulty in drawing conclusions as regards the catecholamine production from the actual content of the gland is illustrated by experiments on resynthesis in animals. Thus there might be a considerable release without any marked reduction of the content of the gland in many cases but also, as during insulin hypoglycemia, when the gland is largely depleted of its catecholamines (22). For this reason it seems of interest to pursue chronic experiments on secretion during exposure to cold. This may be done by estimating the excretion in urine in conjunction with estimations of the amine content in the gland in parallel experiments. By comparing the output of catecholamines in urine as a result of infusion or injection of known amounts of the same amines, the secretion of adrenaline from the adrenals corresponding to a known output in urine could be computed (22).

ADDENDUM

Chronic experiments on rats exposed to cold have indicated that catecholamines are strongly involved in the acclimation process as recently found by Dr. J. Leduc in our laboratory (to be published in *Acta physiol. scandinav.*, 1960).

REFERENCES

1. Cannon, W. B., *Bodily Changes in Pain, Hunger, Fear and Rage.* New York: Appleton, 1915.
2. Cannon, W. B., A. Querido, S. W. Britton and E. M. Bright. *Am. J. Physiol.* 79: 466, 1927.
3. Satow, Y. *Tohoku J. Exp. Med.* 30: 561, 1937.
4. Wada, M. and E. Fuzii. *Tohoku J. Exper. Med.* 37: 505, 1940.
5. Cramer, W. *Observations on the Functional Activity of the Suprarenal Gland in Health and in Disease.* Sixth Scientific Report on the investigations of the Imperial Cancer Research Fund. London, 1919.
6. Vincent, S. *Quart. J. Exper. Physiol.* 15: 319, 1925.
7. Kayser, C. *Ann. physiol.* 15: 1087, 1939.
8. Fisher, E. R., B. Fisher and F. J. Fedor. *Proc. Soc. Exper. & Biol. Med.* 89: 140, 1955.
9. Hillarp, N. A. and B. Hökfelt. *Acta physiol. scandinav.* 30: 55, 1953.
10. Morin, G. *Rev. can. biol.* 5: 388, 1946.
11. Schaeffer, G. *Bull. acad. méd. (Paris)* 130: 587, 1946.
12. Wada, M., M. Seo and K. Abe. *Tohoku J. Exper. Med.* 26 381, 1935.
13. Saito, S. *Tohoku J. Exper. Med.* 11: 544, 1928.
14. Itikawa, K. *Tohoku J. Exper. Med.* 27: 68, 1935.
15. Nagakura, I. *Tohoku J. Exper. Med.* 50: 39, 1949.
16. Long, C. N. H. *Recent Prog. in Hormone Research* 1: 99, 1947.
17. Manger, W. M., K. G. Wakim and J. L. Bollman. *Chemical Quantitation of Epinephrine and Norepinephrine in Plasma.* Springfield: Thomas, 1959.
18. Des Marais, A. and L. P. Dugal. *Can. J. Med. Sci.* 29: 90 1951.
19. Hökfelt, B. *Acta physiol. scandinav.* 25, Suppl. 92, 1951.
20. Hsieh, A. C. L. and L. D. Carlson. *Am. J. Physiol.* 190: 243, 1957.
21. Suomalainen, P. and V. J. Uuspää. *Nature. London* 182: 1500, 1958.
22. Bydgeman, S., U.S. von Euler and B. Hökfelt. *Acta physiol. scandinav.* 49: 21, 1960.

Adjustments of the adrenal cortex and thyroid during cold acclimation[1]

O. HEROUX
Division of Applied Biology, National Research Council, Ottawa, Canada

HEROUX, O. *Adjustments of the adrenal cortex and thyroid during cold acclimation.* Fed. Proc. 19, Suppl. 5: 82–85. 1960.—An increased secretion of corticosteroids has been demonstrated by many authors in animals suddenly exposed to cold. In chronic exposure to cold in the laboratory, however, there is increasing evidence in the literature of a return towards the initial normal level in the activity of the adrenal cortex, while the thyroid remains hyperactive. Under the more natural fluctuating environmental conditions prevailing outdoors during the winter, the adrenal cortex of white rats exposed to cold for three months has been found to secrete *in vitro* at a faster rate than in the summer controls, while the thyroid appeared to be degenerating. In view of the metabolic effects of the thyroid and adrenal hormones, the endocrine adjustments observed under the two different environmental conditions suggest different metabolic pathways leading to similar capacities for heat production.

IN RECENT YEARS, POSSIBLE DIFFERENCES between the endocrine adjustments required in white rats for survival in a laboratory cold room on the one hand and under the normal seasonal changes on the other have been demonstrated.

It is the purpose of this paper to review the information available on the adjustments of the adrenal cortex and thyroid in chronic exposure to constant cold temperature in the laboratory and exposure to fluctuating cold environmental conditions in nature.

THERMAL ACCLIMATION

It is now generally accepted that the adrenal cortex is specifically involved in the initial response to cold (1). An increased secretion of corticosteroids has been demonstrated by many authors in animals suddenly exposed to cold. Adrenalectomized animals have been shown to be unable to survive if left in a cold room (2). Whether such an increased secretion persisted in animals maintained in a cold environment for a prolonged period, and whether it was essential for the development or maintenance of cold acclimation, was uncertain until 1951 when Sellers, You and Thomas (2) showed that cold-acclimated rats after adrenalectomy could be maintained in the cold for long periods by giving a constant but relatively small amount of cortical extract daily (30 dog units). This observation suggested that much less cortical hormone was required for survival after the animals were acclimated to cold than at the beginning of the cold exposure. It was shown (3) by the eosinophil response to ACTH that the activity of the adrenal cortex in cold exposed rats reaches a maximum in about 20 days and then returns to its preacclimation level (fig. 1).

Subsequently, Rossiter and his co-workers (4) have shown that the increase in the incorporation of inorganic phosphate labeled with radioactive phosphorus P^{32} into the inorganic phosphorus of the adrenal gland was less in rats acclimated to cold than in rats acclimatized to 22°C when both groups were exposed to −5°C for 2 hours (fig. 2). While this test indicates that the adrenal cortex response to a cold temperature shock is less after cold acclimation than before, it says nothing about the state of activity of the adrenal cortex of the rats kept at their acclimation temperature.

Therefore, in an attempt to evaluate this level of activity, in collaboration with Dr. Schönbaum from Toronto, we have measured the *in vitro* production rate of corticosteroids in adrenals of warm and cold-acclimated rats. After 3 months of continuous exposure to 30°C or 6°C the adrenals of those animals were incubated in a Krebs-Ringer bicarbonate glucose medium for 1 hour. Subsequently, the medium was extracted with methylene dichloride and corticosteroids were measured by their absorption at 240 mμ (5).

On an absolute basis, the amount of steroids produced was about the same in both groups (table 1). But since the adrenals were significantly bigger or heavier in the 6°C acclimated rats, and since there was a significant correlation between the amount of steroids produced and the weight of the adrenal, we could calculate with the established equations the steroids production for a common adrenal weight. We found this production rate to be significantly less in the cold-acclimated rats.

Since water content determination and area measurements of the different zones reveal that the increase in weight of the adrenal in cold-acclimated rats is due exclusively to an increase in size of the fasciculata zone (table 2) and since this increase in size is due to a 25% increase in the number of cells (table 3), the lower steroid production per unit weight in cold-acclimated rats must be because each cell is secreting at a slower rate in

[1] Contribution from the Division of Applied Biology, National Research Council, Ottawa, Canada; issued as N.R.C. No. 5961.

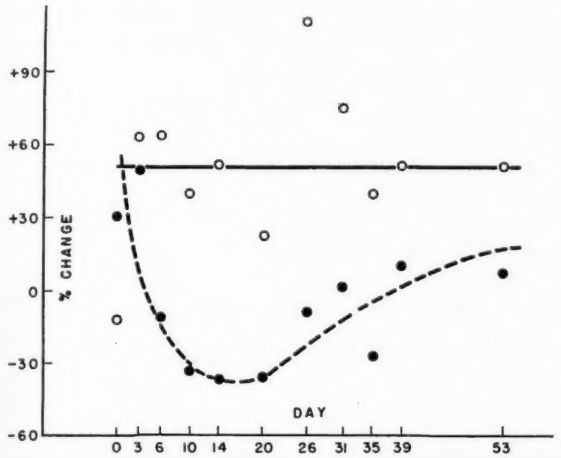


FIG. 1. Eosinophil response as a measure of adrenal cortex activity. Percentage changes in eosinophil counts after injection of one IU of ACTH in rats exposed to 30°C (*open circles*) and 6°C (*solid circles*) for various periods up to 53 days. Curves are hand-fitted.

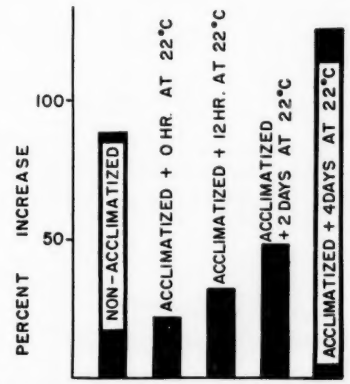


FIG. 2. Effect of acclimatization on the adrenal response to cold exposure. Percentage increase in relative specific activity of adrenal inorganic P of nonacclimatized rats exposed to −5°C for 2 hr. was found to be 88%; rats acclimatized for 4 wk. to 3°C were either transferred directly to −5°C for 2 hr. or else returned to 22°C for 12 hr., 2 days or 4 days before exposure to −5°C. From Rossiter *et al.* (4).

cold- than in warm-acclimated rats. With such an increase in the number of fasciculata cells, it is surprising that the adrenal cortical response should not be greater in cold- than in warm-acclimated rats after exposure to the same cold stimulus, as shown by Rossiter and his collaborators. Although there is a greater number of fasciculata cells in the cold acclimated rats, the total quantity of steroids produced per hour *in vitro* is about the same in cold- as in warm-acclimated rats.

These results suggest that an increase in secretion of corticoids is not essential for maintenance of cold acclimation. Apparently it is not even essential for development of cold resistance since it is possible to develop a certain degree of cold acclimation in adrenalectomized rats

TABLE 1. *In Vitro Adrenal Steroid Production in White Rats*

	No. of Observations	Steroids/Hr. per Animal μg	Steroids/Hr. for Common (47.6 mg) Adrenal* μg
Indoors			
30°C	12	7.43±0.62	7.81±0.45
6°C	12	6.33±0.40	5.95±0.45
Diff.		1.10±0.70	1.86±0.65†
Outdoors			
Summer	12	8.12±0.66	7.76±0.45
Winter	12	10.11±0.45	10.40±0.45
Diff.		1.99±0.88†	2.64±0.45†

* Regression coeff.: 0.087. † Statistically significant at the 5% level.

provided the animals are exposed to cold gradually and intermittently (6).

The decreased adrenal response to cold after cold acclimation has been tentatively attributed to an alteration in the sensitivity of the mechanism, nervous or otherwise, by which the pituitary is stimulated, because after cold acclimation the adrenal cortex responds normally to ACTH, Pitressin or adrenaline indicating clearly that the sensitivity of the hypothalamic-pituitary-adrenal system to a given stimulus is normal (7). But maintenance of body weight after adrenalectomy with a lower dose of cortical extract in cold- than in warm-acclimated rats (8) suggests rather a reduced corticosteroid requirement after cold acclimation (fig. 3).

As far as the thyroid activity is concerned, it has been convincingly demonstrated by Carlson and his collaborators that in rats continuously kept in individual cages at 5°C, the thyroid activity gradually increases and remains high even after 180 days of exposure (9, 10).

SEASONAL ACCLIMATIZATION

Under the fluctuating seasonal conditions prevailing outdoors, the endocrine adjustments in the white rats acclimatized to the cold winter temperatures appeared to be quite different (5, 11). In rats exposed outdoors in groups of 10 during 3 months, the *in vitro* steroid production appeared to be greater in the winter than in the summer rats (table 1) even though there was no hyperplasia of the fasciculata zone of the adrenals of the winter-exposed rats (table 2). In these winter rats, the thyroid showed a very inactive picture, while in the indoor cold-exposed rats, in which the adrenal cortex appeared normally active, the thyroid showed all the histological signs of a great activity. Those thyroid activities were estimated by Dr. A. Des Marais from Ottawa who used a new staining method that has been developed in his laboratory by himself and Dr. Q. N. La Ham (12). With proper stain and radioautographs, they have been able to demonstrate that follicles containing yellow colloid are not secreting active hormones while the follicles containing blue colloid are secreting active iodinated hormones. By counting the number of blue- or yellow-stained follicles, by estimating the

TABLE 2. *Adrenal Weight and Areas of Adrenal Zones*

	No. of Observations	Weight for Common (428 gm) Body Wt.*	Water Content	Areas × 45² mm²			
				Total	Glomerula	Fasciculata	Reticularis	Medulla
		gm	%					
Indoors								
30°C	5	39.7±2.5	65.3±1.2	12070±453	1172±21	4386±460	4304±251	2208±160
6°C	6	53.2±2.3	66.6±1.2	14323±414	1193±67	6427±420	4363±229	2340±146
Diff.		13.5±3.4†	1.3±1.6	2253±614†	21±70	2041±623†	59±340	132±216
Outdoors								
Summer	6	50.0±2.3	67.4±1.2	13670±969	1237±20	5350±582	4560±391	2523±190
Winter	8	48.7±2.6	67.4±1.2	13588±839	1184±58	5588±504	4416±339	2275±165
Diff.		1.3±3.6	0.0±1.6	82±1281	53±770	144±517	144±517	248±251

* Regression coeff.: 0.069. † Statistically significant at the 1% level.

amount of secretion droplets in the epithelial cells, by measuring the height of those cells, and by the infiltration of connective tissue between the follicles, it is possible to estimate the relative activity of a gland.

The thyroids of the 30°C acclimated rats were typical of moderately active glands; the follicles, which were predominantly yellow, were surrounded by much connective tissue, with few secretion droplets in the epithelial cells, and an average cell height of 7 μ. The thyroids of both the '6°C rats' and the 'outdoor summer rats' were on the other hand typical of highly active glands: there were numerous blue follicles surrounded by little connective tissue; secretion droplets were abundant in the cytoplasm and the cell height averaged 15 μ. Finally, the picture of a degenerating gland infiltrated with connective tissue, with empty spaces where follicles had disintegrated, could be seen in the thyroids of the winter outdoor rats; the remaining follicles were predominantly yellow, and the cells were flat (7 μ). The thyroids of the outdoor winter rats showed either this picture or that of a slowly active gland.

TABLE 3. *Number of Fasciculata Cells and Size of Nuclei*

	No. of Observations	Total No. of Cells × 10^{-1}	Diameter of Nuclei μ
Indoors			
30°C	5	3556±247	6.7±0.10
6°C	6	4459±226	6.9±0.09
Diff.		903±335*	0.2±0.13
Outdoors			
Summer	6	4547±225	6.4±0.16
Winter	8	4422±209	6.9±0.15
Diff.		125±307	0.5±0.23*

Total number of cells is cells/mm² × the area of the whole fasciculata zone. † Statistically significant at the 5% level.

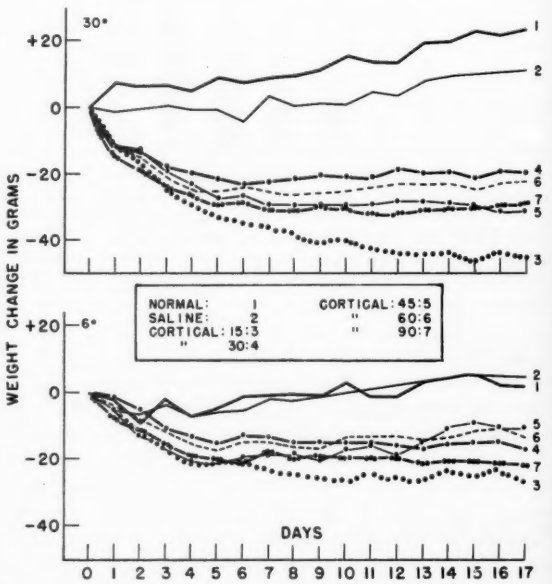


FIG. 3. Weight trends after adrenalectomy of 30°C and 6°C acclimated rats maintained at their respective acclimation temperatures and treated for 17 days with different doses of cortical extract (Wilson Laboratories).

DISCUSSION

Outdoor winter-acclimatized rats, in which cold resistance and peak metabolic rates are just as great as that in 6°C acclimated rats, have therefore inactive thyroids and hyperactive adrenal cortices. In the indoor 6°C rats, the reverse is true, the thyroid is hyperactive and the adrenal cortex is hypoactive. In spite of this, both groups of rats show parallel metabolic adjustments with respect to the change from shivering to nonshivering mechanism of heat production. It might be possible that in cold environments the corticosteroid requirement returns to normal only when the thyroid has attained a certain level of hyperactivity. Boulouard (13) has reported recently that after 6 hours at 5°C the 17-hydroxycorticosteroid level in plasma is higher in thyroidectomized rats than in normal rats and that the increased secretion of corticosterone is somewhat less in thyroidectomized than in normal rats.

In view of the metabolic effects of the thyroid and cortical hormones, the endocrine adjustments observed under those two sets of cold environmental conditions suggest different metabolic pathways leading to similar capacities for heat production.

In summary, there seems to be very little doubt now that while the adrenal cortex is specifically involved in the initial response to cold, it is not essential for maintenance of cold acclimation; it is not even essential for development of a certain degree of cold resistance, provided the animals are exposed to cold gradually and intermittently. Under the fluctuating seasonal conditions prevailing outdoors, however, adrenal cortex appears to remain hyperactive while the thyroid degenerates.

In view of this recent information, some of the problems that require solutions now are the following:

a) Does the type of corticoid secreted by the adrenal cortex change during acclimation to cold?

b) Is the proportion of corticosterone and 17-hydroxycorticosteroid the same in indoor cold-acclimated rats which have a hyperactive thyroid and in outdoor cold acclimatized rats which have an inactive thyroid?

c) Why is the thyroid hyperactive in indoor cold-acclimated rats and not in outdoor cold acclimatized rats?

This last question is the most important, as great emphasis is put on the thyroid hyperactivity in cold acclimation.

REFERENCES

1. SELLERS, E. A. *Rev. can. biol.* 16: 175, 1957.
2. SELLERS, E. A., S. S. YOU AND N. THOMAS. *Am. J. of Physiol.* 165: 431, 1951.
3. HEROUX, O. AND J. S. HART. *Am. J. of Physiol.* 178: 453, 1954.
4. ROSSITER, R. J. AND D. NICHOLLS. *Rev. can. biol.* 16: 249, 1957.
5. HEROUX, O. AND E. SCHÖNBAUM. *Canad. J. Biochem. & Physiol.* 37: 1263, 1959.
6. HEROUX, O. *Am. J. Physiol.* 181: 75, 1955.
7. NICHOLLS, D., R. MOLLOY, K. STAVRAKY AND R. J. ROSSITER. *Canad. J. Biochem. & Physiol.* 37: 671, 1959.
8. HEROUX, O. AND J. S. HART. *Am. J. Physiol.* 178: 449, 1954.
9. COTTLE, M. AND L. D. CARLSON. *Endocrinology* 59: 1, 1956.
10. WOODS, R. AND L. D. CARLSON. *Endocrinology* 59: 323, 1956.
11. HEROUX, O., E. SCHÖNBAUM AND A. DES MARAIS. *Fed. Proc.* 18: 67, 1959.
12. LA HAM, Q. N. *Histochemical Studies on the Thyroid of the Male Albino Rat* (Thesis) Library of Faculty of Science, University of Ottawa, Oct. 1959.
13. BOULOUARD, R. *Comp. rend. soc. biol.* 153: 203, 1959.

Adrenocortical function in rats exposed to low environmental temperatures[1]

E. SCHÖNBAUM

Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada[2]

SCHÖNBAUM, E. *Adrenocortical function in rats exposed to low environmental temperatures.* Fed. Proc. 19, Suppl. 5: 85–88. 1960.—Measurements of corticosteroid formation *in vitro* can be used for the assessment of adrenocortical function in rats subjected to a variety of treatments. Acute exposure to cold causes a transient rise in adrenocortical activity during the first 30 minutes of exposure. If rats are kept in a cold environment for several weeks, an increased activity of the adrenal cortex is first observed but later the adrenocortical activity becomes somewhat reduced.

THE ADJUSTMENTS OF THE ACTIVITY of the adrenal cortex during acclimation to low environmental temperatures have just been discussed by Heroux (1). This author has indicated clearly that a direct assessment of adrenocortical function in the dynamics of acclimation to cold would be very desirable. To obtain at least semiquantitative information we have studied the rates of secretion by the rat adrenal *in vitro* of material which absorbs ultraviolet light and is soluble in methylene chloride. This is a fairly nonspecific measurement of the secretion of corticosteroids. It is desirable to use an *in vitro* approach because many factors other than secretion determine the peripheral blood level of steroids. Of the processes mentioned in table 1 the role of the liver should be stressed. Yates and associates (2) have shown that hepatic steroid inactivation is a major factor in the regulation of adrenal function. Increased thyroid activity will accelerate the reduction of the steroids by the liver and hence indirectly will cause adrenal hypertrophy (3).

Concerning the *in vitro* studies of adrenal activity it is proposed to discuss first very briefly the principle of the

[1] Supported in part by Grants DRBC 9310-07 and 9325-10 from the Defence Research Board of Canada.

[2] Present address: Dept. of Pharmacology, University of Toronto.

TABLE 1. *Adrenal Steroids*

Process	Organ	Control
Secretion	Adrenal cortex	Pituitary, perhaps thyroid, gonads
	Certain tumors	?
Circulation	Blood (plasma) (bound, free)	Heart
Effects	Various organs	?
Inactivation	Mainly liver	Partly by endocrine and metabolic factors
Excretion	Mainly kidney	?

in vitro technique. It is based on the ability of adrenal tissue to form steroids *in vitro* (4). An increased response when ACTH is added to the incubation medium indicates that the output of steroids *in vitro* is not limited by the availability of endogenous substrates.

The disadvantages of the use of an *in vitro* technique are manifold. There is, in the first place, the question whether *in vitro* studies will reflect the events taking place *in situ*. This point is discussed in the section on Results. Furthermore, circulation through intact tissue is replaced by diffusion through tissue slices. Blood is replaced by a synthetic medium (5, 6). This may not be as satisfactory as blood itself. Membrane permeabilities may be altered and it is possible that substances may enter or leave the cells in an unphysiological manner (7, 8). In isolated fragments of adrenocortical tissue, the rate of formation of steroids is much lower than in the perfused gland. The factors mentioned above may afford an explanation of this difference. The major reason for the choice of the *in vitro* system for the study of steroid production in the rat is that it is not possible to obtain adrenal venous blood without severe surgical trauma. This will cause a sudden release of ACTH and activation of the adrenal cortex (see list of effects of ACTH on the adrenal cortex, below). Any effect of exposure to cold or of any other chronic treatment may be altered, hidden or reversed by this 'acute interference.' Another consideration in favor of choosing steroid formation *in vitro* as an index of adrenal activity is that all experiments are carried out on a comparative, not on an absolute, basis and that assessment of steroid formation is the only direct index of the activity of the adrenal cortex (see list below).

Some Effects of ACTH on the Adrenal Cortex

Increased formation of pregnenolone from cholesterol
Depletion of ascorbic acid
Depletion of cholesterol
Increased content of adenosine 3′,5′-monophosphate
Depletion of glycogen
Activation of carbohydrate metabolism
Activation of phosphate metabolism
Activation of nucleic acid metabolism
Increased cellular activity
Increased adrenal weight

METHODS

Male Wistar rats were used throughout. After the rats had been treated according to the requirements of the particular experiment, they were decapitated. The adrenals were removed rapidly, cleaned, weighed and quartered. The adrenal quarters were preincubated for 30 minutes, the Krebs-Ringer bicarbonate-glucose medium was removed and the tissue fragments incubated in fresh medium for one hour. The medium only was extracted with methylene chloride and the ultraviolet absorption of this extract measured at 240 mμ. This rather nonspecific method of estimating corticosteroids is indicative of the total amount of substances with a Δ^4-3-ketone group (4, 9).

RESULTS AND DISCUSSION

Saffran and associates have demonstrated that surviving rat adrenal tissue (halved or quartered glands) incubated appropriately is able to form corticosteroids and retains its responsiveness to corticotrophin (ACTH). A very useful assay for ACTH (4) as well as several studies of adrenal intermediary metabolism (5, 7, 10, 11) have been based on this finding. The measurement of adrenocortical secretory activity *in vitro* would be a very useful tool for the comparative studies of adrenocortical activity or of blood levels of ACTH, in spite of a number of important factors limiting the usefulness of this technique (see first paragraph of this paper). It would have to be shown, however, that the rate at which incubated adrenal tissue forms corticosteroids (without added ACTH) is related to the secretory activity of the adrenal cortex at the moment of its removal or to the blood level of ACTH at the moment of decapitation. A good indication that this relationship exists was obtained in this laboratory some time ago (9). Figure 1 illustrates the results of this study, together with data on blood levels of ACTH obtained by Brodish and Long (12).

The four graphs of figure 1 show blood levels of ACTH, adrenal ascorbic acid concentrations and steroid formation *in vitro* under conditions of acute stress. The data on blood ACTH, published by Brodish and Long (12), refer to the effects of unilateral adrenalectomy on blood ACTH and adrenal ascorbic acid up to 3 hours after the operation. The data from this laboratory (9) concern the effect of histamine on steroid formation *in vitro* and on on adrenal ascorbic acid. The parallelism between blood ACTH and steroid formation is rather striking. Initially, for about 30 minutes, increased blood ACTH and steroid formation *in vitro* are observed, but after 3 hours the values are lower than at zero time.

It has been concluded from this experiment that the *in vitro* technique may be used to study changes of the adrenocortical activity in the intact rat, although the possibility is not excluded that the method may not be sensitive enough to detect very small changes.

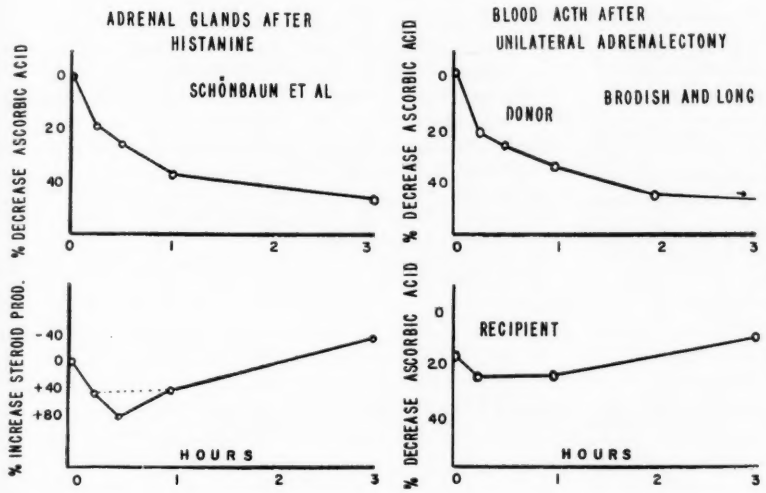


FIG. 1. A comparison of the time course of adrenal ascorbic acid depletion and steroid formation *in vitro* in histamine-treated rats with that of adrenal ascorbic acid depletion and blood corticotrophin in unilaterally adrenalectomized rats. Values were taken from (9) and (12). Brodish and Long (12) assayed blood corticotrophin by measuring the adrenal ascorbic acid depletion in hypophysectomized (recipient) rats after infusing blood from adrenalectomized (donor) rats. Note the parallelism between rates of steroid formation *in vitro* and levels of blood corticotrophin. From Schönbaum *et al.* (9).

Figure 2 indicates the effects of acute, severe cold (deep freeze), on steroid formation *in vitro* and on adrenal ascorbic acid. Only a very brief increase in adrenal steroid formation has been observed. In the experiments on the effects of histamine and on the effects of cold there has been a depletion of adrenal ascorbic acid (figs. 1 and 2). These experiments indicate that measurements of adrenal ascorbic acid levels are very useful for ACTH assays under carefully standardized conditions but that they do not necessarily indicate actual adrenal activity. Once the adrenal ascorbic acid has been depleted, further changes in blood ACTH or adrenocortical activity cannot be detected by this method. For this reason adrenal ascorbic acid levels were not measured in studies of the long-term effects of exposure to a cold environment.

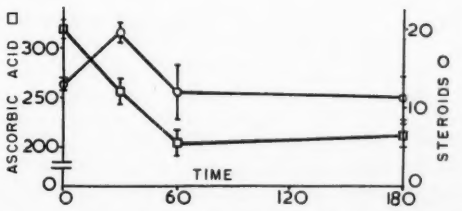


FIG. 2. The effect of acute, severe exposure to cold on adrenocortical activity. Values were taken from (9). Note the different patterns of the rates of steroid formation *in vitro* and the adrenal ascorbic acid concentrations.

The results of studies of long-term exposure of rats to 0°–2°C in a cold room are summarized in figure 3. Figure 3 shows the relationships between body weight, adrenal weight and steroid formation *in vitro* (per unit adrenal weight and per 'total' adrenal weight) of cold-exposed rats and of their age controls. All values are expressed as a percentage of the mean control values. The variations encountered in this study have been enormous. As the problem of variations has been discussed extensively during this Symposium, further elaborations of this point are not necessary. It is sufficient to say that the figures indicate a trend.

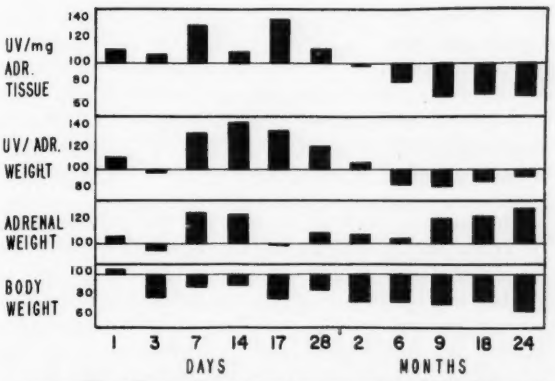


FIG. 3. The effects of long-term exposure to a cold environment on adrenocortical activity. All values are expressed as a percentage of the mean control values.

In agreement with Heroux's results (1), we have found a somewhat reduced adrenal activity in rats exposed to cold for several months, though in the present experiments there was an initial increase in adrenal activity. Degenerative changes of some adrenocortical cells might provide one speculative interpretation of this finding (E. A. Sellers, personal communication).

It appears possible that the adrenal activities expressed per total glandular weight could be described, at least in the first 2 months, in terms of a difference of two exponential functions $Ae^{-k_1 t} - Be^{-k_2 t}$, which is followed by a subsequent equilibrium at a below-normal level. As logarithmic functions in general suggest changes depending on amounts present at any particular moment, the observations could be interpreted tentatively as hormonal effects. This idea, derived from a rather superficial statistical inspection, is in fairly good agreement with the impressive body of physiological information presented by Heroux and associates (1).

REFERENCES

1. HEROUX, O. (This Symposium) *Fed. Proc.* 19, Suppl. 5: 82, 1960.
2. URQUHART, J., F. E. YATES AND A. L. HERBST. *Endocrinology* 64: 816, 1959.
3. YATES, F. E., J. URQUHART AND A. L. HERBST. *Am. J. Physiol.* 195: 373, 1958.
4. SAFFRAN, M. AND A. V. SCHALLY. *Endocrinology* 56: 523, 1955.
5. SCHÖNBAUM, E., M. K. BIRMINGHAM AND M. SAFFRAN. *Canad. J. Biochem. & Physiol.* 34: 527, 1956.
6. BIRMINGHAM, M. K., F. M. ELLIOTT AND P.H.-L. VALÈRE. *Endocrinology* 53: 687, 1953.
7. SCHÖNBAUM, E., M. DAVIDSON, R. E. LARGE AND W. G. B. CASSELMAN. *Canad. J. Biochem. & Physiol.* 37: 1209, 1959.
8. LOPEZ, E., J. E. WHITE AND F. L. ENGEL. *J. Biol. Chem.* 234: 2254, 1959.
9. SCHÖNBAUM, E., W. G. B. CASSELMAN AND R. E. LARGE. *Canad. J. Biochem. & Physiol.* 37: 399, 1959.
10. KORITZ, S. B. AND F. G. PÉRON. *J. Biol. Chem.* 230: 343, 1958.
11. HAYNES, R. C., JR., S. B. KORITZ AND F. G. PÉRON. *J. Biol. Chem.* 234: 1421, 1959.
12. BRODISH, A. AND C. N. H. LONG. *Endocrinology* 59: 666, 1956.

Ascorbic acid in cold acclimation[1]

ANDRÉ DESMARAIS
Department of Biology, University of Ottawa, Ottawa, Canada

ASCORBIC ACID IS ONE OF THE SUBSTANCES universally present in cells, generally believed to be essential in cellular metabolism, but the role of which is still to be determined.

According to recent reports, more particularly from Kersten *et al.* (1), it appears that ascorbic acid is closely related to electron transport and oxidative phosphorylation (2). It has also been shown to influence the metabolism of thyroid hormones (3, 4) and the CoA concentration in the liver (5), and to affect the metabolism of catecholamines and the biosynthesis of steroid hormones (6–10). Some effects have also been reported by Lyon (11) on the carbohydrate and fat metabolism. However interesting these results, they contribute little to the understanding of the role of ascorbic acid in cold acclimation.

Our work in this field has followed the demonstration by Dugal and his colleagues (12) of the increased needs for ascorbic acid in animals exposed to cold, not only in the rat, but also in guinea pigs and monkeys. At the time we undertook this work, it was becoming more and more evident that the thyroid and its hormones, along with adrenaline and noradrenaline, had a major role in cold acclimation (13–21), while the contribution of the adrenal cortex appeared that of a support of the metabolic changes leading to adaptation (22, 23).

Working with guinea pigs on a scorbutogenic diet (24), we observed: *a*) that the animals exposed to cold retain proportionately more ascorbic acid in their tissues when they receive less; *b*) that only those on the lowest daily intake of ascorbic acid show a significant increase in both adrenal weight and thyroid activity (cell height). Since adrenal hypertrophy is generally considered an ordinary consequence of cold stress, one can suppose that ascorbic acid administration, favoring acclimation and suppressing the alarm reaction, has some extra-adrenal action. True, another experiment (25) has shown us that ascorbic acid administration decreases the activity of the thyroid in rats exposed to cold. One of the likely hypotheses for explaining the beneficial effects of ascorbic acid in animals exposed to cold was that its effects could be accounted for at the level of either the thyroid or its hormones. A later experiment (26) showed us that ascorbic acid administration does not seem to have any effect on the response of the thyroid to injected TSH, neither in the cold nor at room temperature. It thus appeared that we were justified in concentrating our efforts on a study of a possible peripheral relationship between ascorbic acid and the thyroid hormones in animals exposed to cold.

If the beneficial effects of ascorbic acid in animals exposed to cold are to be related to the thyroid hormones, what would then be the role of the adrenal cortex? What would be the relationship between the adrenals and the thyroid? These questions have been partly answered by some of our experiments. We observed (27) that the catabolic effects of cortisone, enhanced by exposure to cold, are reversed by the simultaneous administration of thyroxine. Not only is the cortisone unable to maintain animals in a cold environment, but it has deleterious effects in the absence of thyroid hormones. Moreover, these experiments emphasized the fact that ascorbate administration is without effect in the presence of cortisone, whereas it appears to enhance the anticatabolic action of thyroxine.

[1] All work referred to under the author's name was sponsored by Defence Research Board of Canada Grant No. 9310-66.

Was this really a conditioning effect of ascorbate on thyroxine? Another experiment was designed to find an answer to this question (28). The results obtained on thyroidectomized rats show that the daily administration of 10 μg of thyroxine reverses the catabolism, increases survival and maintains the thymus and adrenal weights within normal limits, a degree of protection which a dosage of only 3 μg cannot provide. Moreover, the administration of ascorbate along with the smaller dose of thyroxine produces effects which are comparable to those obtained with the larger dose of the hormone, while ascorbate alone is without effect.

The data obtained so far appear to provide some experimental basis to our initial hypothesis in that the beneficial effects of ascorbic acid in animals exposed to cold seem to be mediated through the thyroid hormones. All the results obtained not only point to the thyroid hormones as a target for ascorbic acid but bring additional support to the conclusion already outlined (22, 23) that the cortical hormones would not play a leading role in cold acclimation. This last point was further stressed by the results of another experiment (28) where it was observed that a certain degree of acclimation and resistance to cold could be obtained in adrenalectomized rats receiving minimal amounts of cortical hormones (cortisone and DCA). Similar evidence was obtained by Egdahl *et al.* (29) on adrenalectomized dogs exposed to cold without any corticoid supplementation.

The accumulated evidence suggests that the adrenal response to cold stress is a sign of nonadaptation. It cannot be denied that adrenocortical hyperfunction can, to a certain degree, favor cold acclimation; however, this mechanism would represent a second line of defence used in case of absolute deficiency of the thyroid and then would usually be unsuccessful. It might also serve temporarily in situations where the thyroid is relatively deficient by permitting the organism to adjust to the new environment until the thyroid is able to meet the demand for increased secretion.

Concerning the relationship between the thyroid hormones and ascorbic acid, it is possible that enzymatic reactions are involved since the thyroid hormones have been shown by Gemmill (30) to enhance the activity of the ascorbic acid oxidase. On the other hand, Dugal and Rangnecker have shown that both exposure to cold and ascorbic acid administration accelerate the metabolism of tyrosine and phenylalanine, precursors of thyroid and medullary hormones (31).

An alternative explanation to the prevention of adrenal hypertrophy by ascorbate administration in animals exposed to cold is that, besides an enhancement of the activity of the thyroid hormones, there would be a decrease in the biological decay of the corticosteroids, as suggested by the *in vitro* observations of Bacchus and Debons (32).

Finally, let us review the evidence presented by Nicholls (33) concerning the relations between the thyroid and cortical hormones. These experiments show that ascorbic acid administration does not decrease the activity of the adrenal cortex in rats exposed to cold; this would tend to minimize the value of the preceding hypothesis based on Bacchus' findings. On the other hand, the adrenal response to ACTH is increased upon ascorbate administration in animals kept at room temperature; this confirms the results of Dugal *et al.* (34–37) and leads one to believe that the activity of the adrenal cortex can be maintained in cold exposed animals without ACTH hypersecretion and adrenal hypertrophy. Nicholls and Rossiter (38) have also shown that a functional thyroid is a prerequisite to adrenal cortex hypersecretion in animals exposed to cold. Their results show that the degree of adrenal hypertrophy is the same in all animals, while the metabolic activity of the gland is reduced only in those being more hypothyroid, all their animals being in a relative hypothyroid state. The authors suggest that the degree of cortical hyperfunction is directly related to thyroid activity. Would there be a dissociation between the secretory activity of the adrenal cortex and its hypertrophy? Would the hypertrophied gland of the hypothyroid animal in the cold be hypofunctional? Such a dissociation was reported by Heroux and Schönbaum, as will be found in this Symposium. In this case, the hypertrophy preventing effect of both thyroxine and thyroxine-ascorbate administration, as observed in our experiments, would be due to the recovery of the normal function of the adrenal cortex. The hypertrophy of the adrenals in cold-exposed animals could then be interpreted as a qualitative deficit in cortical hormones rather than as a quantitative one.

We can see that, if the thyroid hormones now appear as the target for ascorbic acid, the mechanism of this action is far from being understood. In the past few years, considerable progress has been made in the physiology of the thyroid hormones, mostly through the contribution of Pitt-Rivers, Thibault, and Roche and Michel. There seems to be some relationship between the acid derivatives of thyroxine and triiodothyronine and the activation of these hormones at the cellular level. Recently Roche *et al.* (39) have questioned this interpretation; however, their contention is based on a paper by Pitt-Rivers and Thibault (cited by Roche (39)) which is anterior to Thibault's experimental demonstration of the physiological activity of these acid derivatives (40–43). In Pitt-Rivers' opinion (44), this interpretation is still valid. Moreover, confirmation of Thibault's observations has recently been obtained (13), and there is evidence (44) showing that these acid derivatives are normal products of the metabolism of the thyroid hormones.

It has been shown by LeBreton and van Hung (14) that the *in vitro* acetylation of thyroxine and triiodothyronine requires the presence of CoA in the medium. On the other hand, we have already mentioned the fact that the CoA content of the liver is increased in animals exposed to cold (5, 45), increase which is enhanced by the addition of ascorbic acid in the diet (5). The possibility of a relationship between ascorbic acid, CoA and the acetylation of the thyroid hormones is now being investigated in our laboratory, as one of the many possible explanations of the beneficial effects of ascorbate administration in animals exposed to cold.

XUM

REFERENCES

1. KERSTEN, H., W. KERSTEN AND H. STAUDINGER. *Biochim. et biophys. acta* 27: 598, 1958.
2. LEHNINGER, A. L., M. UL HASSAN AND H. C. SUDDUTH. *J. Biol. Chem.* 210: 911, 1954.
3. SEALOCK, R. R., R. L. GOODLAND, W. N. SUMERWELL AND J. M. BRIERLY. *J. Biol. Chem.* 196: 761, 1952.
4. LADU, B. N. AND D. M. GREENBERG. *Science* 117: 111, 1953.
5. CAMPBELL, J., G. R. GREEN, E. SCHÖNBAUM AND H. SOCOL. *Fed. Proc.* 17: 22, 1958.
6. ROSTON, S. *Fed. Proc.* 17: 136, 1958.
7. BACCHUS, H. *Am. J. Physiol.* 188: 297, 1957.
8. SLUSHER, M. A. AND S. ROBERTS. *Endocrinology* 61: 98, 1957.
9. PERIC-GOLIA, L., E. N. KRISTEN AND R. S. JONES. *Fed. Proc.* 18: 499, 1959.
10. MASON, H. S., *et al.* Cited by P. TALALAY in *Physiol. Rev.* 37: 362, 1957.
11. LYON, J. B., JR. *Fed. Proc.* 18: 278, 1959.
12. DUGAL, L. P. *Cold Injury, 2nd Conference.* New York: Macy, 1952, p. 85.
13. SAUNDERS, H. L., D. NUSS, C. M. GREENBERG, A. ZAVALYDRIGA AND E. VAN LOON. *Proc. Soc. Exper. Biol. & Med.* 100: 61, 1959.
14. LEBRETON, L. AND M. L. VAN HUNG. *Compt. rend.* 242: 1357, 1956.
15. HSIEH, A. C. L. AND L. D. CARLSON. *Am. J. Physiol.* 188: 40, 1957.
16. SCHAEFFER, G. AND O. THIBAULT. *Compt. rend. soc. biol.* 139: 857 and 859, 1945.
17. THIBAULT, O. *Rev. Can. Biol.* 8: 3, 1949.
18. SWANSON, H. *Endocrinology* 59: 217, 1956.
19. RING, G. C. *Am. J. Physiol.* 137: 582, 1942.
20. HSIEH, A. C. L. AND L. D. CARLSON. *Am. J. Physiol.* 190: 243, 1957.
21. HSIEH, A. C. L. AND L. D. CARLSON. *Am. J. Physiol.* 190: 247, 1957.
22. HEROUX, O. AND J. S. HART. *Am. J. Physiol.* 178: 449, 1954.
23. SELLERS, E. A., S. S. YOU AND N. THOMAS. *Am. J. Physiol.* 165: 481, 1951.
24. DES MARAIS, A. AND P. M. GAGNON. *Compt. rend. soc. biol.* 149: 1714, 1955.
25. DES MARAIS, A. *Compt. rend. soc. biol.* 149: 214, 1955.
26. DES MARAIS, A. *Canad. J. Biochem. & Physiol.* 36: 1099, 1958.
27. DES MARAIS, A. *Canad. J. Biochem. & Physiol.* 33: 1018, 1955.
28. DES MARAIS, A. *Canad. J. Biochem. & Physiol.* 34: 1251, 1956.
29. EGDAHL, R. M., M. HUME AND J. B. RICHARDS. Res. Report, Proj. NM 007 081.22.10, Nav. Med. Inst., Nat. Nav. Med. Center, Bethesda, p. 391.
30. GEMMILL, C. L. *Am. J. Physiol.* 167: 349, 1951.
31. DUGAL, L. P. AND P. V. RANGNECKER. *Canad. J. Biochem. & Physiol.* 36: 185, 1958.
32. BACCHUS, H. AND A. F. DEBONS. *Fed. Proc.* 15: 6, 1956.
33. NICHOLLS, D. *Canad. J. Biochem. & Physiol.* 34: 919, 1956.
34. DUGAL, L. P., A. DES MARAIS AND P. M. GAGNON. *Canad. J. Biochem. & Physiol.* 33: 677, 1955.
35. DUGAL, L. P. AND M. THÉRIEN. *Science* 115: 598, 1952.
36. DUGAL, L. P. AND M. THÉRIEN. *Ann. endocrinol.* 13: 578, 1952.
37. DUGAL, L. P. AND M. THÉRIEN. *Compt. rend.* 234: 245, 1952.
38. NICHOLLS, D. AND R. J. ROSSITER. *Endocrinology* 56: 547, 1955.
39. ROCHE, J., R. MICHEL, J. NUMEZ AND C. JACQUEMIN. *Endocrinology* 65: 402, 1959.
40. THIBAULT, O. *Ann. endocrinol.* 17: 35, 1956.
41. THIBAULT, O. *Ciba Foundation Colloquia*, 1956.
42. THIBAULT, O. *Archiv. sci. physiol.* 10: 423, 1956.
43. THIBAULT, O. *Compt. rend. soc. biol.* 151: 475, 1957.
44. PITT-RIVERS, R. AND J. R. TATA. *The Thyroid Hormones.* New York: Pergamon, 1959, pp. 156, 157.
45. BRUMLEVE, S. J. AND R. D. OLSON. *Fed. Proc.* 18: 19, 1959.

Metabolic function of ascorbic acid in acclimation to cold[1]

DOROTHY JARED HOIJER

Department of Physiology, University of California School of Medicine, Los Angeles, California

HOIJER, DOROTHY JARED. *Metabolic function of ascorbic acid in acclimation to cold.* Fed. Proc. 19, Suppl. 5: 90–93. 1960.—The essential role of ascorbic acid in acclimation to cold has been affirmed by numerous experimental studies. The increased need for adrenaline and noradrenaline in the cold can be met in part by the ascorbic acid stimulated hydroxylation of their aromatic precursors. Likewise, the hydroxylation of corticosteroids is stimulated by ascorbic acid to provide an adequate supply of the hormones necessary for increased substrate utilization and to combat the conditions of stress. Finally, the role of ascorbic acid in pathways of electron transport has been presented with reference to its possible function in effecting increased oxidation without concurrent increases in phosphorylation.

[1] This work was supported by Research Grants C-3103 and C-3635 from the National Cancer Institute, National Institutes of Health, and in part by grants from the University of California Cancer Research Coordinating Committee.

THE IMPORTANT ROLE OF ASCORBIC ACID in acclimation to cold has been demonstrated repeatedly, particularly by the detailed studies of Dugal *et al.* (1) and Des Marais (2). However, the exact metabolic function of this vitamin has been difficult to define.

The hypertrophy of the adrenal glands of animals ex-

posed to cold can be prevented by the administration of ascorbic acid, without a concurrent decrease in the enhanced secretory activity characteristic of the cold stimulated state (3).

The rat synthesizes ascorbic acid in increased amounts when exposed to cold as determined in various tissues. The kidneys of rats at 0°C for 3 months contain 50%, and the liver 40%, more ascorbic acid than controls at room temperature (4). The adrenal ascorbic acid is increased 160% in 28 days at 4°C (5). The brown fat of rats at room temperature contain 119 μg of ascorbic acid per gram of tissue. After 117 days at 5°C the concentration is 353·7 μg/gm of tissue (6). The livers of the rat, mouse, rabbit, dog and pig convert D-glucuronic acid to L-ascorbic acid, but in the guinea pig, which cannot synthesize ascorbic acid, the liver does not have the enzymes necessary for these conversions (7, 8). When exposed to cold, the guinea pig, in particular, conserves a greater than normal proportion of the ingested vitamin by a process associated with a decreased excretion in the urine.

The initial response to cold in both the guinea pig and rat is associated with a sharp drop in adrenal ascorbic acid levels, with recovery to normal within 48 hours; this is followed by a gradual increase to a maximum at 10 days, after which a plateau is maintained at levels well above normal (5). The high levels of ascorbic acid in the liver, kidney, brown fat and adrenals of cold-acclimated animals would thus appear to fulfill some metabolic function necessary to survival (9). This is accentuated by the fact that animals that die during acclimation studies have been found to contain subnormal levels of ascorbic acid (3).

The close correlation between adrenal function and ascorbic acid has been the subject of investigation for years and is of particular interest in the study of cold acclimation. Administered ACTH causes a marked and immediate fall in the ascorbic acid content of the adrenal glands (5, 10). Cholesterol, as the precursor of the corticosteroids, likewise decreases with ACTH treatment (11). Hypophysectomized rats given ACTH show a parallel release of ascorbic acid and corticosterone into the venous effluent of the adrenal gland. However, the amount of ascorbic acid released is not as great as the amount disappearing from the adrenal gland (12, 13). This would indicate some utilization of the compound in the metabolic functions of the adrenals.

Whole-animal studies of the effect of ascorbic acid on the utilization of the amino acids, phenylalanine and tyrosine, were made with rats on normal and ascorbic acid-supplemented diets. The blood plasma levels of phenylalanine and tyrosine were reduced when ascorbic acid was added to the diet. Likewise, subjecting the animal to cold decreased the plasma concentration of these amino acids; and cold plus ascorbic acid lowered the plasma levels below that of either condition alone (14). From these observations one could infer a more rapid utilization of these metabolites with increased ascorbic acid concentration and the stress of cold.

Ascorbic acid-deficient humans injected with 30 grams of L-tyrosine show a tyrosuluria which can be abolished by the administration of ascorbic acid (15). Likewise, if guinea pigs are maintained on a vitamin C deficient diet and injected with tyrosine, the excretion of homogentisic acid increases. Addition of adequate ascorbic acid to the diet can eliminate this abnormality (16). Since homogentisic acid is found in the urine of patients with the metabolic aberration of alkaptonuria, this is of clinical interest.

The use of ascorbic acid by the adrenal medullary tissue in the hydroxylation of aromatic compounds was first demonstrated by Udenfriend *et al.* (17). In this experimental work, ascorbic acid was oxidized to dehydroascorbic acid in the formation of hydroxytyramine from tyramine. The pathway of the conversion of C^{14}-labeled phenylalanine to tyrosine, DOPA, DOPE, noradrenaline and adrenaline was earlier delineated by Udenfriend (18) and Gurin and Dellugia (19). The end product, adrenaline, was protected from oxidation by adequate levels of ascorbic acid.

The hydroxylation of the aromatic ring, as stimulated by ascorbic acid, is specific to the para position of the benzene ring and is different in nature from the more generally encountered free radical hydroxylation, which is random in nature. The ascorbic acid hydroxylation occurs first on the aromatic ring, before the more vulnerable side chain is hydroxylated (20). When C^{14}-labeled phenylalanine was incubated with the whole adrenal gland for 2 hours, pH 5.3 and 37°, 600 μg/gm of tissue were converted to tyrosine. When the cortex was incubated with phenylalanine 450 μg of the substrate were converted to tyrosine, while the medulla converted 950 μg/gm of tissue. The addition of 10 mg of ascorbic acid to the incubation medium increased these conversions severalfold (21). Significantly, the hydroxylation of the aromatic ring, as stimulated by ascorbic acid, utilizes molecular oxygen rather than the hydroxyl radical of water; moreover the hydroxyl radical which is added to the ring is not interchangeable with water (22, 23). In the process of hydroxylation of phenylalanine to the catecholamines by perfused calf adrenals, there is 86% reduction in the conversion if the process is carried out anaerobically rather than aerobically (24), which emphasizes the importance of molecular oxygen in this reaction.

The adrenal medulla granules store the catechol amines, which are discharged upon stimulation of the splanchnic nerve (25, 26). The 'intact isolated' adrenal medulla synthesizes only minute quantities (24) of the catecholamines relative to the amount stored in the tissues (5 mg/gm). In contrast, the 'intact isolated' adrenal cortex synthesizes, within 2 hours, 10 to 30 times as much of the corticosteroids as is stored in the tissues (0.01 mg/gm). If the adrenal cortex is perfused with the precursors of the corticosteroids, the ratio of the amount produced to the amount stored is raised to 100 times the original content in the tissues (24). This is probably one reason that ascorbic acid disappearance

has been associated with adrenal cortical rather than medullary activity. However, it should be emphasized that ascorbic acid is also important in the synthesis of the catecholamines. Thus, in the cold, ascorbic acid would be important in the production of required amounts of adrenaline and noradrenaline.

As has been mentioned earlier, the administration of ACTH produces a release of ascorbic acid into the adrenal effluent with a parallel release of corticosterone. Experimental work has shown that with adrenal mitochondrial preparations from swine, the hydroxylation of the 11β position of the benzene portion of the indole ring of desoxycorticosterone is increased from 8% to 20% when 10 mg of ascorbic acid is added to the incubation medium (27). Ascorbic acid stimulates the conversion of the non-oxy to the oxy-corticosteroids, but does not appear to be involved in the production of DOCA from its precursor (24). In the hydroxylation of DOCA to corticosterone, as stimulated by ascorbic acid, or other substances known to carry on this function, the transfer of hydrogen is made directly to oxygen to form the active OH^- radical which then hydroxylates the 11β position of the benzene ring without attacking the more vulnerable pyrole ring (20, 22). That the oxygen of this OH^- radical is from molecular oxygen has been shown with O_2^{18} incubated in a system of TPNH and adrenal cortex. TPNH can serve as the source of hydrogen, but the reaction is much more rapid if a small quantity of DPNH is also present (23, 24, 28).

In the hydroxylation of steroids, it has been found that ascorbic acid is the active agent, whereas dehydroascorbic acid is completely inactive (28). It should be noted that ascorbic acid undergoes a pH-dependent, rapidly reversible oxidation-reduction reaction involving the transitory monodehydroascorbic acid radical which is capable of either accepting or losing electrons. This therefore represents the active form of ascorbic acid (29, 30).

The maintenance of the active monodehydroascorbic acid in biological systems is dependent upon two factors, i.e., the level of the oxidant and that of the reductant. Ascorbic acid oxidase is present in most mammalian tissues and transforms ascorbic acid to the monodehydro form. The enzyme itself contains copper but may be inactivated by excessive levels of inorganic copper. Inorganic copper also oxidizes ascorbic acid to the dehydroascorbic acid and to further oxidation products. Thus by the chelation of free inorganic copper in biological systems, thyroxine prevents both the inactivation of the ascorbic acid oxidase as well as the destruction of ascorbic acid (31–33). Adequate levels of thyroxine are therefore important for the maintenance of the active form of ascorbic acid.

Likewise, the concentrations of reductants of the system, particularly DPNH and TPNH, are necessary for the stability of ascorbic acid. With artificial ACTH *in vivo* stimulation, or experiments *in vitro*, uncontrolled pH conditions would lead to inadequate concentrations of reductants. This could account for the conflicting reports on the disappearance of ascorbic acid in the adrenal tissue and venous effluent after stimulation with cold or ACTH. In systems with optimum pH, a very small amount of ascorbic acid can act as an electron transport coenzyme in the oxidation of DPNH (30, 34).

The effects of ascorbic acid on the transfer of electrons, with DPNH as the reducing agent and oxygen as the electron acceptor, have been measured in systems containing homogenates (35), mitochondria (28) or microsomes (30, 34). The mitochondria were washed repeatedly until no trace of endogenous DPNH and only 1% of the original concentration of ascorbic acid could be observed. The latter amount appeared tightly bound and could not be removed. The effects of increasing concentrations of ascorbic acid upon the reduction of DPNH were measured by the extinction coefficient of DPNH. The value of the latter with mitochondria alone was 0.4; the addition of 2.5 μmoles of ascorbic acid reduced this to 0.32, and 50 μmoles brought it to 0.05 in the same period of time. The effect of ascorbic acid upon DPNH reduction was also measured in the Warburg in an aerated system containing well washed mitochondria, DPNH and ascorbic acid. The respiration of mitochondria alone was 1 mm^3 at 150 minutes; DPNH increased this to 10 mm^3, and the addition of 5 μmoles ascorbic acid accelerated the uptake of oxygen to 150 mm^3. In a mitochondrial system with both DPNH and cytochrome *c*, the rate of reaction can be greatly accelerated by the addition of ascorbic acid. Without ascorbic acid the extinction coefficient of DPNH is reduced from 0.4 to 0.1 in 30 minutes. With the addition of 10 μmoles of ascorbic acid the extinction coefficient falls to 0.01 in 19 minutes (28).

Since the oxygen uptake of mitochondria can be stimulated twofold by the microsomal elements of the tissue cell, further inquiry into this phase of cellular metabolism seems pertinent (36). It is of interest that ascorbic acid is synthesized in the microsomes and that the greatest amount of this vitamin is concentrated in the cytoplasm (87%–95%); thus it is available to either the microsomes or the mitochondria (7, 37, 38).

Kersten and Staudinger (34) identified an ascorbic acid-dependent DPNH oxidase in the microsomes of adrenals from swine, which was not inhibited by KCN, sodium azide or antimycin A. The adrenal microsomes were also tested for activity with DPNH, cytochrome b_5 and ascorbic acid in an aerobic system. The microsomes alone showed no respiration and oxidized DPNH only very slowly. Cytochrome b_5 increased the oxygen uptake to 85 mm^3, and the addition of 0.5×10^{-3} moles ascorbic acid accelerated the oxidation to 180 mm^3. In these experiments as in earlier work, the ascorbic acid was present in the reduced form, with the monodehydroascorbic acid as the active radical. With DPNH omitted from the system, ascorbic acid was quickly oxidized to dehydroascorbic, as determined by ascorbic acid analyses (30).

The oxidation of DPNH by way of the microsomal DPNH-ascorbic acid-cytochrome b_5 pathway is slower

than the mitochondrial-cytochrome *c* oxidase system, but the former is inhibitor resistant and nonphosphorylating (30, 36). Ascorbic acid can also increase the rate of reduction of cytochrome *c* in a mitochondrial system without a concurrent increase in phosphorylation (39, 40). The availability of ascorbic acid in the microsomes and cytoplasm would appear to be important in cellular metabolism involving the nonphosphorylating microsomal-DPNH-ascorbic acid-cytochrome b_5 pathway of electron transport, and also as a catalyst to the mitochondrial-cytochrome *c* electron transport system. In cold-acclimated animals, with their demonstrably increased concentrations of ascorbic acid, these functions could provide a means by which oxygen uptake might be increased without an increase in phosphorylation.

In conclusion, we would like to emphasize that ascorbic acid can stimulate three processes essential to homeostasis in reduced environmental temperatures: *1*) the hydroxylation by the adrenal medulla of phenylalanine and tyrosine to the catecholamines; *2*) in the adrenal cortex, hydroxylation of the non-oxy to the oxy-corticosteroids, which have higher gluconeogenic properties and increased transaminase activity; and finally *3*) ascorbic acid can facilitate the transport of electrons to increase the oxidation of substrate without concurrently increasing the phosphorylation.

REFERENCES

1. Dugal, L-P. and G. Fortier. *Canad. J. Biochem. & Physiol.* 35: 169, 1957.
2. Des Marais, A. *Rev. Can. Biol.* 16: 189, 1957.
3. Dugal, L-P. and M. Thérien. *Endocrinology* 44: 420, 1949.
4. Dugal, L-P. and M. Thérien. *Can. J. Research* 25: 111, 1947.
5. Katsh, S., G. F. Katsh and P. Osher. *Am. J. Physiol.* 178: 457, 1954.
6. Pagé, E. and L-M. Babineau. *Can. J. Research* 28: 196, 1950.
7. Hassan, M. and A. L. Lehninger. *J. Biol. Chem.* 223: 123, 1956.
8. Bublitz, C., A. P. Grollman and A. L. Lehninger. *Biochim. et biophys. acta* 27: 221, 1958.
9. Booker, W. M., F. M. DaCosta, J. R. Tureman, C. Froix and W. Jones. *Endocrinology* 56: 413, 1955.
10. Sayers, M., G. Sayers and L. A. Woodbury. *Endocrinology* 42: 379, 1948.
11. Des Marais, A. *Can. J. Med. Sci.* 30: 157, 1952.
12. Slusher, M. A. and S. Roberts. *Endocrinology* 61: 98, 1957.
13. Briggs, F. N. and W. Toepel. *Endocrinology* 62: 24, 1958.
14. Rangneker, P. V. and L-P. Dugal. *Canad. J. Biochem. & Physiol.* 35: 185, 1958.
15. Crandon, J. H., B. Landau, S. Mikal and J. Balmanno. *New England J. Med.* 258: 105, 1958.
16. Sealock, R. R. and H. E. Silberstein. *J. Biol. Chem.* 135: 251, 1940.
17. Udenfriend, S., C. T. Clark, J. Axelrod and B. Brodie. *J. Biol. Chem.* 208: 731, 1954.
18. Udenfriend, S. *Biochim. et biophys. acta* 20: 48, 1950.
19. Gurin, S. and A. M. Dellugia. *J. Biol. Chem.* 170: 545, 1947.
20. Brodie, B. B., J. Axelrod, P. A. Shore and S. Udenfriend. *J. Biol. Chem.* 208: 741, 1954.
21. Fellman, J. H. and M. K. Delvin. *Biochim. et biophys. acta* 28: 328, 1958.
22. Talalay, P. *Physiol. Rev.* 37: 362, 1957.
23. Tomkins, G. M., P. J. Michael and J. F. Curran. *Biochim. et biophys. acta* 23: 655, 1957.
24. Rosenfeld, G., L. C. Leeper and S. Udenfriend. *Arch. Biochem. and Biophys.* 74: 252, 1958.
25. De Robertis, E. *Exp. Cell Research* 12: 563, 1957.
26. Carlsson, A. and N. Hillarp. *Acta physiol. scandinav.* 44: 163, 1958.
27. Kersten, H., W. Kersten and H. Staudinger. *Biochem. Ztschr.* 327: 284, 1955.
28. Kersten, H., W. Kersten, and Hj. Staudinger *Biochem. Ztschr.* 328: 24, 1956.
29. Kern, D. M. *J. Am. Chem. Soc.* 76: 1011, 1954.
30. Krisch, K. and H. Staudinger. *Biochem. Ztschr.* 331: 195, 1959.
31. Gemmill, C. L. *Am. J. Physiol.* 167: 349, 1951.
32. Benhamu, N., R. J. Magee and C. R. Dawson. *Arch. Biochem. and Biophys.* 81: 135, 1959.
33. Gemmill, C. L. and R. L. Plunkett. *Arch. Biochem. and Biophys.* 36: 434, 1952.
34. Kersten, H., W. Kersten and H. Staudinger. *Biochim. et biophys. acta* 27: 598, 1958.
35. Radsma, W. *Acta physiol. et pharmacol. neerl.* 5: 330, 1957.
36. Schneider, W. C. *Advances in Enzymol.* 21: 1, 1959.
37. Hagen, P. *Biochem. J.* 56: 44, 1954.
38. Kanfer, J., J. Burns and G. Aschwell. *Biochim. et biophys. acta* 31: 556, 1959.
39. Cooperstein, S. J. *J. Biol. Chem.* 234: 392, 1959.
40. Kielly, W. W. and J. R. Bronk. *Biochim. et biophys. acta* 23: 448, 1957.

Relation of ascorbic acid to adrenocortical function during cold stress

W. M. BOOKER
Department of Pharmacology, Howard University Medical School, Washington, D.C.

BOOKER, W. M. *Relation of ascorbic acid to adrenocortical function during cold stress.* Fed. Proc. 19, Suppl. 5: 94–96. 1960.—Either the fall in adrenal ascorbic acid in acute cold stress seems to be a 'trigger' mechanism for the release of adrenocortical hormone, or ascorbic acid takes part in the formation of the adrenocortical hormone. In adrenal vein effluent the rise of ascorbic acid precedes by several minutes the rise of the adrenocortical hormone. There is no essential change in whole-body ascorbic acid during cold stress. Ascorbic acid: *a*) acts to increase the survival of mice in cold, especially in the presence of either the adrenal gland or the administered cortisone; *b*) decreases the rate of metabolism of the adrenocortical hormone in incubated liver slices; and *c*) facilitates the conversion of C^{14} acetate to cholesterol in the presence of ACTH.

IN OUR LABORATORY we have been interested in cold as an acute stressing agent in order to study the role of ascorbic acid in adrenocortical function. It has long been known that acute exposure to cold stimulates the pituitary-adrenal system, resulting in the increased secretion of ACTH, a fall in adrenal ascorbic acid and the subsequent release of adrenal corticoids. The fall in adrenal ascorbic acid following ACTH secretion (or administration) is used by Sayers (1) as an assay method for ACTH. The role of ascorbic acid in adrenocortical function, however, remains unanswered despite many communications in this connection. We have expressed the view that the fall in adrenal ascorbic acid may represent a 'trigger' for the release of adrenocortical hormone from the adrenal and that ascorbic acid may be facilitating metabolic activity and other functions of the adrenocortical hormones (2). Slusher and Roberts (3), on the other hand, believe that ascorbic acid takes part in the synthesis of adrenocortical hormone either as a high energy source or as a source of hydroxyl groups.

In this paper data will be presented supporting our points of view as well as that of others which may vary from ours. All, or most all of the data presented have already been published. Proper acknowledgement and clearance for use of the material has already been obtained by the authors and publishers. No details on methods will be given, but reference to the published papers will be made.

Figure 1 shows the changes in adrenal ascorbic acid and cholesterol following the exposure of groups of rats to cold (5°C). It may be noted that both adrenal ascorbic acid and cholesterol decrease, but the ascorbic acid returns to normal level at about 12 hours, while the cholesterol is still decreased at 24 hours. Ralli and Dumm

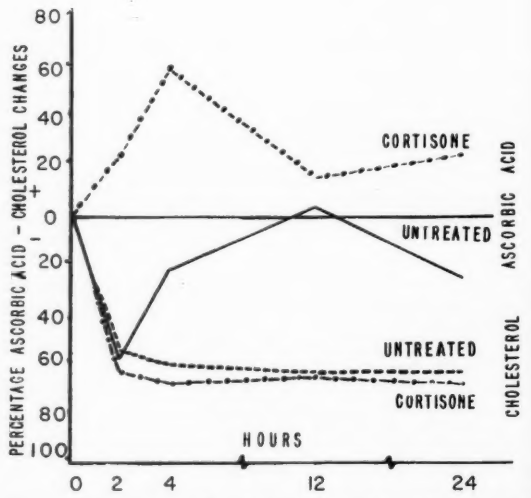


FIG. 1. Changes in adrenal ascorbic acid and cholesterol during stress in 6 untreated and 6 cortisone-treated rats. Unstressed, untreated rats at room temperature constituted the controls. Statistical analysis: ascorbic acid-treated against untreated—2 hr. $P = 0.01$; cholesterol, cortisone-treated against untreated—2 hr. $P = 0.01$.

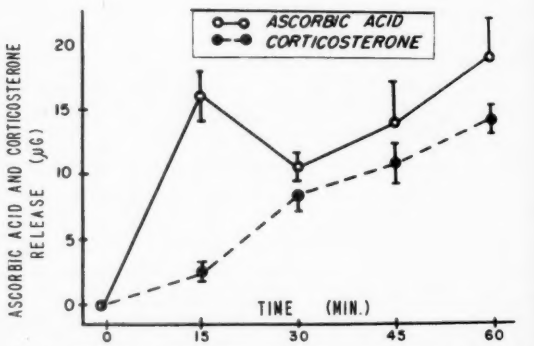


FIG. 2. Changes in ascorbic acid and corticosterone in adrenal vein effluent following administration of ACTH to hypophysectomized rats. From Slusher and Roberts (3).

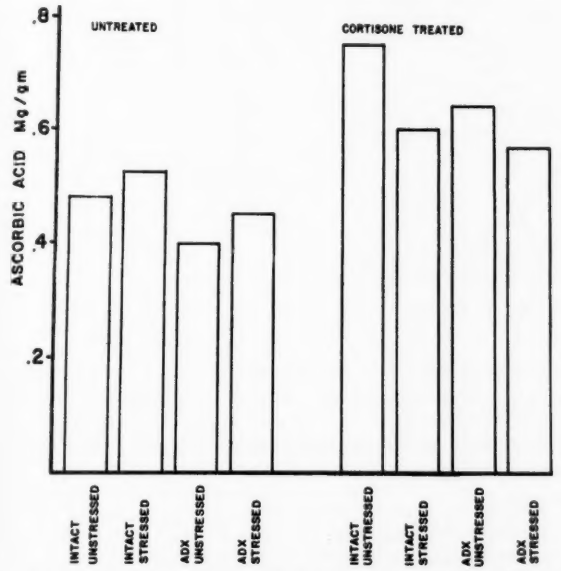


FIG. 3. Effects of ascorbic acid on the survival of 80 intact and adrenalectomized mice. Statistical analysis at 3rd hour: intact against adrenalectomized untreated, $P = 0.01$; adrenalectomized untreated against adrenalectomized treated, $P = 0.01$; intact, untreated against adrenalectomized treated, $P = 0.01$.

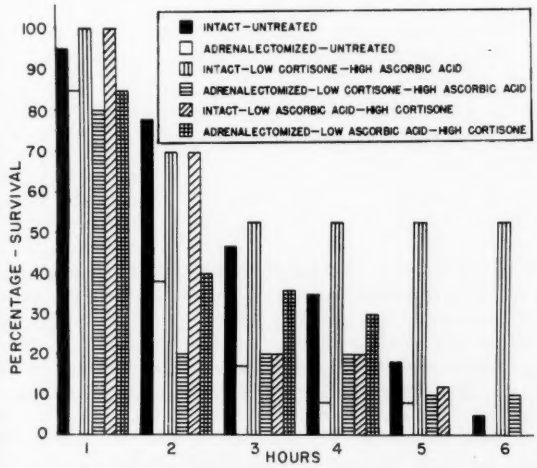


FIG. 4. Effects of combined dosages of ascorbic acid and cortisone on survival of 40 intact and adrenalectomized mice. Statistical analysis at 3rd hour: low ascorbic acid–high cortisone against adrenalectomized similarly treated, $P = 0.02$; high ascorbic acid–low cortisone intact against adrenalectomized animals similarly treated, $P = 0.02$.

(4) have shown that cholesterol requires between 24 and 48 hours for return to a normal level in the adrenal. More will be said later on the relation of ascorbic acid to cholesterol synthesis in the adrenal. It is of interest that the cortisone treated animals exhibited an increase in adrenal ascorbic acid rather than a fall. This is indirect evidence that the fall in ascorbic acid precedes (and may be necessary for) the synthesis or release of adrenocortical hormones. Indeed this is borne out by the work of Slusher and Roberts (3), as shown in figure 2. The adrenal vein ascorbic acid effluent rises upon administration of ACTH some 15 minutes before the adrenocortical hormone rises. A lag seems to exist, therefore, between adrenal ascorbic acid decrease and hormone release from the gland. We have alluded to this lag (5).

The fall in adrenal ascorbic acid is not accompanied by a fall in ascorbic acid from other tissues as pointed out by Sayers (1). Likewise, we have seen that there is no essential difference between the whole-body ascorbic acid of stressed mice and unstressed mice. This would seem to indicate that there is rapid resynthesis in order that the adrenal ascorbic acid may be restored after about 12 hours following stress. We have shown in animal and human studies that cortisone raises the renal threshold to ascorbic acid; this would facilitate higher adrenal storage.

The role of ascorbic acid in survival of mice in cold is shown in figure 3. Ascorbic acid-treated intact mice survive longer than untreated; and the survival is comparable to that of animals treated only with cortisone. Note, however, that ascorbic acid is not as effective in adrenalectomized as in intact animals. This suggests that there is some functional tie-up between adrenocortical hormones and ascorbic acid. Figure 4 shows how combinations of ascorbic acid and cortisone act in survival of cold-stressed mice. These results offer further evidence for the view that a relationship exists between the adrenocortical hormones and ascorbic acid. Note that small doses of cortisone plus high doses of ascorbic acid are more effective in intact animals than in adrenalectomized animals where the reverse is true.

Glutathione is closely related to whatever functional tie-up there may be between adrenocortical hormones and ascorbic acid. Figure 5 shows that glutathione administered to intact animals is effective in increasing their survival to cold. Note that it is much less effective in adrenalectomized animals. It has been suggested that glutathione functions to keep ascorbic acid in the reduced state in which it is most effective in its physiological or pharmacological role. There is no evidence that glutathione itself stimulates the pituitary adrenal system.

The influence of ascorbic acid on the metabolism of the adrenocortical hormones may well be a major role that ascorbic acid plays in the relationship between this hormone and the vitamin. For example, Bacchus and Lampkin (6) have shown that liver slices from ascorbic acid-deficient guinea pigs (up to 20 days) metabolize the side chain of 17-OH corticosterone at a much faster rate than slices from normal animals. When ascorbic acid is added to the ascorbic acid-deficient slices, the rate of metabolism is considerably slower.

A discussion of the role of ascorbic acid in adrenocortical function would be incomplete without some

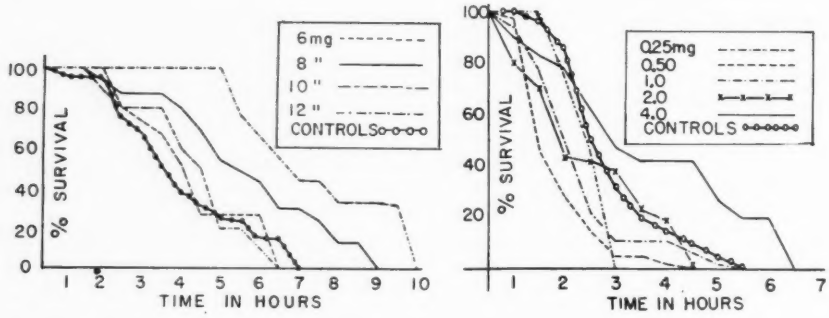


FIG 5. Effects of glutathione on survival of intact and adrenalectomized mice subjected to cold stress.

mention of the relationship between ascorbic acid and cholesterol and the conversion of cholesterol to corticoids. Hechter and Pincus (7) and others have established this pathway with reasonable clarity. We have seen in our laboratory that the conversion of C^{14} acetate to cholesterol in incubated adrenal slices in the presence of ACTH moves faster when ascorbic acid is added to the medium than when ACTH is present alone.

REFERENCES

1. SAYERS, G. *Endocrinology* 37: 96, 1945.
2. BOOKER, W. M. *Am. J. Physiol.* 181: 2, 1955.
3. SLUSHER, M. AND S. ROBERTS. *Endocrinology* 61: 98, 1957.
4. RALLI, M. W. AND E. P. DUMM. *Fed. Proc.* 13: 38, 1954.
5. BOOKER, W. M. *Endocrinology* 56: 413, 1955.
6. BACCHUS, H. AND J. LAMPKIN. *Endocrinology* 57: 531, 1955.
7. HECHTER, O. AND G. PINCUS. *Physiol. Rev.* 34: 459, 1954.

Discussion

L. D. CARLSON, O. HEROUX, S. A. D'ANGELO, W. H. COTTLE, D. G. BAKER, R. E. SMITH, E. SCHÖNBAUM, A. D. KELLER, A. DESMARAIS, E. DE ROBERTIS, K. M. KNIGGE, E. J. MASORO, R. E. BEYER

DR. CARLSON: There are two reflections I have had about adrenaline and noradrenaline. First, I want to thank Professor von Euler for the way in which he put the questions into good focus. We have been concerned with metabolism in general but one must also think about the metabolism of the hormone itself. Dr. von Euler suggested to me in a conversation that perhaps noradrenaline is being methylated in the animal, and that this is what has happened in terms of the calorigenic action. We also have given thought to the interaction with other hormones. One intriguing aspect is that with this calorigenic change there is the change in peripheral circulation. Have we some common denominators here? By far the most intriguing fact is that there is, in response to the same stimulus to the animal, a shift from the shivering response to what we call a nonshivering response. This means a change in terms of the mechanism. Perhaps a study of fever or work with pyrogens will be of value.

DR. HEROUX: I would like to make some comments regarding Dr. Cottle's paper. Although it has been shown quite convincingly by the biologic decay method that the thyroid hormonal output remains higher than normal in rats kept at 5°C for 60 days, it does not necessarily mean that Schackner's observation of a normal thyroid activity in rats kept at 15°C for 40 days simply indicates that the cell height method which he used was not sensitive enough. Actually, it is quite possible that the thyroid returns to a normal level of activity after 40 days at 15°C but not after 60 days at 5°C. There are in the literature other evidences which certainly suggest that under certain circumstances the homeothermic state can be maintained with no involvement of the thyroid. For example, after cold acclimation, thyroidectomized animals can survive with only 2.5 μg of thyroxine (1); we have also reported at this Symposium that white rats kept outdoors during the winter in groups of 10 can have a greater metabolic response to cold than their summer controls even if their thyroids are almost completely degenerated; finally it has been observed by many people that hibernators kept in a cold room can maintain homeothermy without any increase in the activity of their thyroids as measured by the cell height method (2). K. M. Knigge (3) has indeed observed an increased thyroid activity in cold-exposed hamsters as reflected by the radioiodine trapping which was 10 times as great as that observed in control animals while, histologically, the thyroid gland exhibited a progressive decrease in epithelial cell height. The discrepancy between the two methods might however be due to the fact that the observations on thyroid histology were made on ani-

mals kept under 8 hours of light per day while the observations on the iodine uptake were made on other animals maintained under continuous light. Since the experimental conditions were different it is hardly fair to compare the two methods. In Rand's (4) as well as in Steven's experience (5) the cell height method agreed very well with more direct methods such as thyroxine replacement after thiouracil treatment and biologic decay.

Another comment that I would like to make is that on reviewing the literature of the last 50 years, it is possible to find at least 70 references on the effect of cold environment on thyroid activity, which many times appear contradictory. But if the references are classified according to the types of animals (mammals, birds, hibernators) and according to the environmental conditions (continuous cold exposure in the laboratory or outdoor cold exposure in nature), it becomes apparent that in mammals continuously exposed to cold in the laboratory or in birds in nature which apparently do not develop a better insulation, the thyroid activity increases, while in mammals running free in nature and which have been shown to develop a better fur insulation, the thyroid activity decreases during the winter even though the metabolism remains elevated (6–9). Hibernators appear to be in a class by themselves; during the winter in nature (10–12) or during cold exposure in the laboratory (13), homeothermy is maintained in nonhibernating periods without any apparent involvement of the thyroids.

Whether the relationship between the thyroid activity and the insulation is real or not, we do not know, but in any event this classification of the different references is certainly helpful in accounting for certain discrepancies in the results obtained by different authors.

Dr. D'Angelo: Restriction of food can influence thyroid function importantly. Deprivation of either water or food or both causes thyroid atrophy and decreased circulating levels of TSH. Even restraint of the animal may affect endocrine function. Experimenters in Germany have captured wild rabbits and restrained them in cages. They claimed that the fright induced a true thyrotoxicosis in these rabbits. With respect to the findings that the histology of the thyroid in winter animals suggests inactivity, I should like to say that this morphological parameter by itself is not sufficient to gain a full picture of the pituitary-thyroid interplay. There may well be important differences in nature as regards endocrine function, but I think a more comprehensive study is required here just as has been done in the laboratory animal. The rather high doses of L-thyroxine used by Dr. Smith in his experiments are ones capable of causing adrenocortical stimulation in the intact animal. In view of the role of the adrenal cortical hormones—permissive or otherwise—I wonder whether it might not be profitable to test conjointly thyroxine and cortical hormones on mitochondrial and particulate fraction activities.

Dr. Cottle: Concerning Dr. Heroux's remarks, I have nothing to add; I am in full agreement with him. In answer to Dr. D'Angelo's question, I used food restriction as a tool to alter thyroid function. I am just testing an hypothesis. Starvation and withholding of water, are closely related; as you realize, if you restrict water the animal doesn't eat. Regarding cold restraint, this was an acute test at the end of the experiment.

Dr. Baker: The total restriction of food, but not water, for animals exposed to cold of 2 °C does not prevent the increase in metabolic rate measured at 2 °C during the first 50 hours of exposure. If you place warm-acclimated (25°–30°C) adult rats at 2 °C without food, they survive on the average 96 hours. Survival time is maximum when the body weight is in the range of 280 to 310 grams (male rats). Heavier or lighter rats tend to die earlier. If you do this with cold-acclimated rats the survival time is slightly, not significantly, prolonged (D. G. Baker and E. A. Sellers, unpublished observations).

Dr. Smith: Dr. D'Angelo's suggestions are certainly very much in order. It is true that the 30-microgram animal may be already in a thyrotoxic condition, and the curves of oxygen utilization of these washed particulate fractions from liver would seem to indicate that these animals are well up toward maximal values at the end of 2 weeks. We have in fact gone to a 30-μg-per-day animal as a test animal for a mildly thyrotoxic system. The further addition of other hormonal materials is an attractive experimental approach and one in which we are very much interested. Our principal limitation, I feel now, is that we do not yet understand the thyroxine treated system sufficiently to justify the further complications entailed on introduction of other agents. The significance of the depressed phosphorylation in the poorly washed mitochondrial fraction, in terms of the *in vivo* state, is an attractive area of speculation. Whether our poorly washed fraction resembles more nearly the homogenate, whether the homogenate has anything to do with the slice, and so on back to the *in vivo* system and intact organism, is really, I think, one of the crucial points of this whole Symposium. We can recognize that we still have a complex system even when we reduce it to what we would like to call its basic parameters. We still don't know what we are doing in those systems. A well-washed mitochondrion does respond, obviously, to thyroxine, but it does not change its oxidative phosphorylation. This means, evidently, that the mitochondrion per se is relying *in vitro* and possibly *in vivo* upon reactions with extra mitochondrial materials in order to allow for this expression of a depressed P/O. Our negative findings in respect to differential ATPase and glucose-6-phosphatase activities in these heterogeneous preparations would tend to reduce the probability of uncontrolled degradative phosphorolysis.

Dr. Schönbaum: I wonder whether Dr. Smith would like to speculate briefly on his finding that thyroxine increases the the TPNH-cytochrome *c* reductase activity of his washings. This fraction presumably would contain many microsomes. This would be in agreement with the observations of Phillips and Langdon (14) who also found hepatic TPNH-cytochrome *c* reductase activity dependent on thyroid function. The activity of DPN-cytochrome *c* reductase was affected comparatively little in these experiments, which included normal, hypophysectomized, thyroidectomized and thyroidectomized thyroxine-treated rats. TPN-diaphorase was not affected. Furthermore, Rudolph and Olsen (15) found that glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase activities of a number of tissues were, at least in part, under endocrine control. Dr. Smith might have some further ideas on the effects of cold exposure or the endocrines on enzyme activities.

Dr. Smith: With respect to your question, Dr. Schönbaum, we initially examined the DPNH-TPNH shunt pathway with the idea that we would thereby establish the case for the depressed P/O which we saw in this poorly washed fraction in the cold-acclimated animal, in terms of the reported effects of thyroxine. Based on the latter, we should expect to obtain a rise in the activity of the TPNH-dependent enzyme systems, and TPNH-cytochrome *c* reductase with a concurrent depression of the TPNH-DPN transhydrogenase. However, in our measurements of these in the M_1 liver fraction from cold-acclimated rats, we found no change in the reductase and only a questionable depression in the transhydrogenase. In that same series we also tested the TPNH-dependent 6-phosphogluconic

XUM

and glucose-6-phosphate dehydrogenases without finding significant departures from normal, and here we would have expected a substantial rise by analogy with the thyroxine effects reported by Glock and McLean (16) on those enzymes. The reasons for these departures are still not clear, but may in part be explained in terms of the age and length of exposure of the animals to cold and the changing metabolic pattern and hormonal mediation under these conditions (cf. Hannon, in this Symposium, p. 100).

Dr. Keller: I would like to underscore Dr. Cottle's questioning the validity of resting energy metabolism measurements in the cold-acclimatized animal, because during the acclimatizing process physiological changes obviously occur other than the probable increase in thyroid activity. The neutral external environment for the unacclimatized animal is not a neutral environment for the acclimatized animal. Cold acclimatization is not the simple equivalent of hyperthyroidism.

Dr. DesMarais: I would like to ask Dr. Cottle or other specialists in the room to explain how they can translate the rate of release of radioiodine from the gland into quantity of hormones secreted. That disturbs me very much. In your experiments, the rates of release are either increased or reduced, but what does it mean exactly in terms of quantity of hormones produced?

Dr. Cottle: I will reply to Dr. DesMarais' remarks first. Of course, these are relative measures, relative rate of loss of the hormone; we do not know the exact quantity. A number of assumptions are made using this method, assuming of course, that the hormone in the gland is tagged. Unless the specific activity of iodine in the gland is known the I^{131} release does not give a measure of the amount of hormone released.

I'd just like to make a remark regarding Dr. Keller's question: Is resting metabolism not the same in both groups of animals? Certainly somebody should run a set of curves and determine the neutral temperature of these animals. I suggest that the resting metabolism would be higher in the cold-acclimated animals considering that tissues like liver from cold-acclimated rats has a higher metabolic rate *in vitro*. Other tissues like muscle do not show much difference. The change in liver Q_{O_2} is probably a reflection of this organ's unique function in handling metabolites required by all tissues. The rate of turnover is greatly increased in the cold. The change we see when we bring animals back into the warm may be a continuation of this process rather than the effect of greater amounts of thyroid hormone.

To come back to the idea of running curves, if this is done we will have the resting metabolism of the two groups at two different temperatures. What have we got then? We then have the animals in different environments.

Dr. D'Angelo: Dr. De Robertis should be complimented for a very fine piece of work on adrenomedullary structure; the problem of glandular secretion is one of the most vexing ones in morphology. His beautiful electron micrographs illustrating the release phase of the catecholamines made me wonder about their production and their relation to the nervous stimulus. Does acetylcholine merely trigger the release of the droplets situated at the periphery of the cell or is it also responsible for the production of the droplets in the inner portion of the cell near the Golgi zone?

Dr. De Robertis: The stimulation of the splanchnic nerve produces the release of the acetylcholine, and certainly this is what induces the release of the adrenaline containing droplet. But we have seen also that even with a very short stimulation of the splanchnic nerve in the rabbit, there is formation of droplets in the inner part of the cell. We have not studied this problem enough, but we think that it will show that probably the same mechanism will also trigger the secretion.

Dr. Knigge: I would like to ask Dr. De Robertis if he has seen different adrenomedullary cell types that may be related to secretion of adrenaline and noradrenaline respectively. Strikingly in the hamster, and in some other species also, one can see tinctorially different cell types; more lightly staining cells are located at the periphery of the medulla.

Dr. De Robertis: With Dr. Sabatini we have been working very hard on this problem in the hamster, because it is known that the center and the outer regions differ in the content or noradrenaline and adrenaline. This has been demonstrated mainly by fluorescent microscopy by Erankö and also by the iodate method of Hillap. Also there are recent reports in the literature indicating that both granules can be separated by different sedimentation rates. Apparently the noradrenaline granules are a little bigger or have higher specific gravity than the adrenaline. However, with the electron microscope we find no evidence so far that there are two types of granules.

Dr. Masoro: Dr. Carlson, this question is directed to you in regard to your opening remarks. If I interpreted them correctly, you implied that the calorigenic action of epinephrine is related to its regulation of phosphorylase activity. I don't see why the enhancement of phosphorylase activity should necessarily lead to an increase in heat production. I wonder if you would comment on this point.

Dr. Carlson: I believe I am correct in saying that, insofar as what we know about the chemical action of epinephrine, it may involve the phosphorylase *a* to *b* conversion. It is interesting that the rise in sugar itself is not the mechanism that is involved, since you can increase blood sugar in other ways without influencing metabolism. The definite link of epinephrine to increased metabolism I am afraid is missing.

Dr. Beyer: I would like to ask Dr. De Robertis if he would care to speculate on possible mechanisms to explain the slides he has shown us. For example, do the droplets start accumulating in the endoplasmic reticular membranes where the RNA particles regulate the synthesis of the droplet components? Is the membrane of the droplet laid down in the Golgi zone, which appears to be essentially endoplasmic reticulum minus the RNA granules? Or is this process just the reverse of what I've asked? Could you trace the intracellular passage of the droplets for us?

Dr. Robertis: Well, this is a question about the origin of secretion which is now very much in the forefront of cytology. We know that in protein synthesis the endoplasmic reticulum has a great deal to do, particularly the ribosomes or small RNA granules, which are certainly involved in the synthesis of protein. However, it may happen that the material which is formed at this level of this endoplasmic reticulum in small molecules is then stored in the region of the Golgi complex. That is what happens, for example, in the pancreas. Apparently the Golgi complex has the function of condensing or segregating this synthesized material within; and probably it also acts by dehydrating the material. The important thing here is that all this happens within a membrane, so that the material, the secretion, is segregated from the rest of the cell. We have here a very active substance, a neurohumoral substance, which is segregated from the rest of the cell. The same thing happens with the synaptic vesicles and also with the secretion of the neurohypophysis.

REFERENCES

1. SELLERS, E. A. AND S. S. YOU. *Am. J. Physiol.* 163: 81, 1950.
2. DEANE, H. W. AND C. P. LYMAN. *Endocrinology* 55: 300, 1954.
3. KNIGGE, K. M. *Anat. Rec.* 127: 75, 1957.
4. RAND, C. G., D. S. RIGGS AND N. B. TALBOT. *Endocrinology* 32: 509, 1943.
5. STEVENS, G. E., A. D'ANGELO, K. E. PASCHKIS, A. CANTAROW AND F. W. SUNDERMAN. *Endocrinology* 56: 143, 1955.
6. EICKHOFF, W. *Arch. path. Anat.* 322: 84, 1952.
7. KRACHT, J. *Acta endocrinol.* 15: 355, 1954.
8. DELOST, P. AND J. NANDY. *Compt. rend. soc. biol.* 150: 906, 1956.
9. HEROUX, O. AND A. DES MARAIS. *Fed. Proc.* 18: 264, 1959.
10. SHOWRON, S. AND S. ZAJAEZEN. *Compt. rend. soc. biol.* 141: 1105, 1947.
11. ZELESKY, M. *Anat. Rec.* 62: 109, 1935.
12. KAYSER, G. AND M. ARON. *Arch. Anat. (Strasbourg)* 33: 21, 1950.
13. DEANE, H. W. AND C. P. LYMAN. *Endocrinology.* 55: 300, 1954.
14. PHILLIPS, A. H. AND R. G. LANGDON. *Biochim. et biophys. acta* 19: 380, 1956.
15. RUDOLPH, G. G. AND N. S. OLSEN. *Biochim. et biophys. acta.* 19: 382, 1956.
16. GLOCK, G. E. AND P. MCLEAN. *Biochem. J.* 61: 390, 1955.

IV

Intermediary Metabolism

Chairman: A. O. M. STOPPANI

Intermediary glucose metabolism in the cold-acclimatized rat[1]

JOHN P. HANNON

Physiology Department, Arctic Aeromedical Laboratory, APO 731, Seattle, Washington

HANNON, JOHN P. *Intermediary glucose metabolism in the cold-acclimatized rat.* Fed. Proc. 19, Suppl. 5: 100–105. 1960.—The effects of 3–4 weeks' cold exposure (5°–1°C) on the activities of glucokinase, glucose-6-phosphatase, glucose-6-phosphate and 6-phosphogluconic dehydrogenases, total phosphorylase, phosphorylase *a* and *b*, phosphoglucomutase and pyruvate formation over the terminal glycolytic span of enzymes were assayed. Various shifts in the pattern of intermediary hexose metabolism as a result of cold exposure are discussed.

WHEN A SMALL MAMMAL SUCH AS A RAT becomes acclimatized to cold, certain alterations in the metabolism of glucose are observed. Thus in the direction of glycogen synthesis, it has been reported (1) that the intact acclimatized rat forms liver glycogen from ingested or injected glucose at much greater rates than control animals. Similar results have been obtained *in vitro* (2) with diaphragm muscle from acute, but not chronically exposed, rats.

In the reverse direction, Hannon and Young (3) have observed that fasting cold-acclimatized rats maintain blood sugar levels as well as do fasting warm-acclimatized rats. In addition, it has been shown that acclimatized rats maintained higher fasting liver glycogen stores than controls (4, 5). Since fasting blood sugar levels are the same under the two environmental conditions, this would seem to indicate that cold exposure leads either to an augmented gluconeogenesis or to a 'sparing action' on carbohydrate stores.

The extent to which glucose catabolism is affected by cold exposure is still somewhat controversial. Thus we have a report (6) that liver tissue from cold-acclimatized animals forms $C^{14}O_2$ from C^{14}-labeled glucose at the same rate as in control animals. In agreement with this observation, lactic oxidase (7) and lactic dehydrogenase (8) activities are found to be unaffected by cold exposure. On the other hand, data exist which indicate a markedly increased sensitivity on the part of the cold-acclimatized animal to epinephrine and especially to norephinephrine-induced thermogenesis (9). In addition, there are considerable data (7, 8) indicating that acclimatization is associated with increased activity of various components of the tricarboxylic acid cycle of liver and muscle tissue. Finally Depocas *et al.* (10) have shown that by comparison with control rats 6°C acclimatized rats, when exposed to −5°C, converted C^{14}-labeled glucose to $C^{14}O_2$ at greater rates immediately after intraperitoneal injection. These investigators, however, also observed that, when measured over a 2.5-hour period, the rate of conversion was the same for both acclimatized and non-acclimatized animals.

From the foregoing reports we can conclude that the cold-acclimatized rat has an augmented capacity both for glucose formation and for its utilization. The latter is not too surprising in view of the fact that these animals consume at least 50% more food (including carbohydrate) than nonexposed animals. However, the fate of this carbohydrate when taken up by the cells is still somewhat uncertain. One may probably assume that part of the augmented utilization includes an increased capacity for glycogen synthesis. On the other hand, one cannot safely assume that an increase in glucose utilization implies a corresponding increase in glucose oxidation. For instance, the possibility exists that a sizable portion of ingested and subsequently glycolyzed glucose might be diverted to amino acids and fats. If this were true, then it would be conceivable that during the postabsorptive period these animals could support

[1] The views expressed are those of the author and do not necessarily represent official Air Force policy. The experiments were conducted according to 'Rules Regarding Animal Care' as established by the American Medical Association. (Air Force Regulation: 160–94).

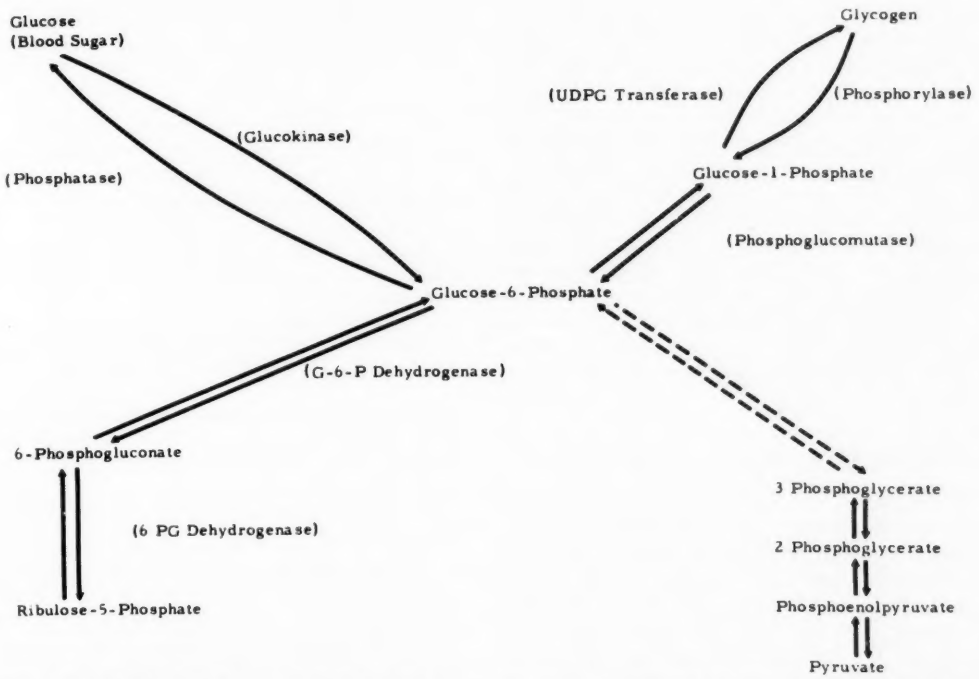


FIG. 1. The effects of cold acclimatization on the glycolytic system of liver and muscle. In both liver and muscle, cold exposure led to an increase in the activity of glucokinase, a decrease in the activities of glucose-6-phosphate dehydrogenase and 6-phosphonic dehydrogenase, and no change in the activity of phosphoglucomutase. Measurements in liver indicated that cold exposure induced increased activities both in glucose-6-phosphatase and the rate of pyruvate formation over the terminal glycolytic span of enzymes.

their high tissue oxidative rates with substrates other than carbohydrates.

We see therefore that we have only a limited body of knowledge on the qualitative and quantitative alterations in carbohydrate metabolism wrought by cold exposure. We have even less knowledge about the mechanisms behind such alterations as are known to occur. The purpose of the experiments to be described here was to investigate how prolonged cold exposure alters certain specific enzyme activities in the glycolytic phase of carbohydrate metabolism. Based on the assumption that the activity or amount of an enzyme *in vitro* is but a reflection of the amount of substrate passing over it *in vivo* (11, 12), we hoped that these measurements would give us some insight not only into the alterations in intermediary carbohydrate metabolism but also into the mechanisms behind them.

For orientation purposes, the specific enzymes or enzyme systems of interest to us in these studies are illustrated in figure 1, a much simplified diagram of glycolysis in which glucose-6-phosphate has been placed as a central component since it has several alternative pathways to follow once it has been formed. However, before discussing the results obtained in these experiments, certain basic concepts regarding the interpretation of data obtained from enzyme activity measurements should be considered.

In determining both the direction and rate of a reversible reaction or series of reactions, three factors are of primary importance: the concentration of reactants, the concentration of products, and the concentration of enzyme or enzymes. For example, when an animal is ingesting a large amount of carbohydrate, glycolysis will proceed in the direction of pyruvate and acetyl-Co A (ignoring glycogen formation). The rate at which this reaction will proceed will depend on the concentrations of glycolytic enzymes, of reactants, and of the reaction products. If food is withdrawn so that the animal must burn fat and protein, reversal of the glycolytic reactions will occur; the former reaction products of glycolysis (pyruvate and acetyl-Co A) now become the reactants, and the former reactants (glucose or glycogen) become the products. Again the several concentrations of enzymes, of reactants, and of products are what determine the rate. With regard to any reversible enzyme, therefore, an increased activity can lead to an increased rate of catalysis in either direction.

In light of these concepts and the central position occupied by glucose-6-phosphate in the glycolytic phase of metabolism, the present data will be considered from the following viewpoints: glucose-6-phosphate to blood sugar interconversion, hexose-monophosphate shunt activity, and terminal glycolytic activity.

In the measurements that follow, the effect of a 1-

month cold exposure (5°–1 °C) on adult male Sprague-Dawley rats was tested. Both liver and muscle enzymes were investigated, first, because together these two tissues account for a sizeable portion of carbohydrate utilized by the animal, and second, because they also represent a sizable portion of the metabolizing or 'thermogenic' mass that is so important during cold exposure. All of the assays were performed either on homogenates of liver and gastrocnemius muscle in 0.25 M sucrose with 0.005 M ethylenediaminetetra-acetic acid (pH 7.4), or more generally, on supernatants derived therefrom by centrifugation at 105,000 × gravity to remove the particulate material. The general methods of tissue preparation as well as those for actual enzyme assay procedures are described in detail elsewhere (13).

TABLE 1. *Effect of Prolonged Cold Exposure on Liver and Muscle Glucose-6-Phosphatase and Glucokinase Activities*

Enzyme	Control			Cold-Exposed			Δ	t
	N	Mean*	S.E.	N	Mean*	S.E.		
Muscle								
Glucokinase	6	0.327	±0.0269	6	0.480	±0.0276	+0.153	3.97
Liver								
Glucokinase	6	0.77	±0.043	6	0.99	±0.050	±0.22	3.33
G-6-Phosphatase	11	7.91	±0.33	12	9.54	±0.29	+1.63	3.86

$P < 0.01$. *Activities are expressed as μmoles of substrate converted per gm of original tissue per min.

GLUCOSE-6-PHOSPHATE–BLOOD SUGAR INTERCONVERSION

As seen in figure 1, two enzymes catalyze the interconversion of free glucose and glucose-6-phosphate, phosphorylation being mediated by glucokinase, and dephosphorylation by glucose-6-phosphatase. Both these enzymes are present in liver, but only the glucokinase is found in muscle. Thus in liver, free glucose can move into or out of the metabolizing system, whereas in muscle, it can move only in one direction, i.e. into the system.

With prolonged cold exposure, the activities of these enzymes were significantly elevated (table 1). In liver tissue, the relative increase of both glucokinase and glucose-6-phosphatase was essentially the same, i.e. 20%–25%. Muscle tissue, on the other hand, exhibited a more pronounced cold effect, the increase being 47%, or approximately twice as great as that observed in the liver tissue enzymes. One should note that the glucokinase activities of both liver and muscle are the lowest of all the glycolytic enzymes studied and are in agreement with the conclusions of others (14) that this reaction is the limiting one in the utilization of free glucose by the tissues.

From these measurements, we can see that the augmented ability of the intact, cold-acclimatized animal to utilize free glucose (1) as well as to maintain blood glucose levels in the fasting state (3) is reflected in activity changes of the appropriate enzymes. At least part of the mechanism behind these phenomena, therefore, seems indicated. This conclusion should be qualified, however, by the fact that the relationship of glucokinase activity to glucose utilization is not a simple matter. A number of other factors are important in determining the rate at which glucose is phosphorylated. Thus while there is considerable evidence (15) that some glucokinase is located in the plasma membrane, there is also evidence that this enzyme is partly located in the particulate fraction of cells (16, 17). Changes in structural relationships of glucokinase in the cell could easily influence the rate of glucose utilization. To date, we have no information on this insofar as cold acclimatization is concerned. In addition, the levels of glucose-6-phosphate, ADP and ATP within the tissue influence glucokinase activity. Thus evidence has been adduced to indicate that glucose-6-phosphate and ADP strongly inhibit (16, 17) and that the ATP and ADP ratio influences the rate of the glucokinase reaction (18). Finally, there is evidence that certain hormones may be acting at the glucokinase level in cold-exposed animals. Thus cold-acclimatized rats exhibit an increased insulin sensitivity (19), and in acutely exposed animals a cold-induced increase in the *in vitro* incorporation of glucose into diaphragm muscle has been reported and has been ascribed to increased thyroid activity of the animal (20). Increased thyroid activity in the cold-acclimatized animal may also be responsible for the elevated activity of the terminal glycolytic enzymes observed here as well as for the uncoupling of oxidative phosphorylation reported elsewhere (21). Together these changes would tend to give an increased rate of glucose utilization by removing glucose-6-phosphate at greater rates.

The increased activity of liver glucose-6-phosphatase, besides indicating at least one of the mechanisms associated with the augmented ability of the cold-acclimatized rat to maintain blood sugar levels in the fasting state (3), also might be predicted on the basis of the high thyroid activity in these animals. Thus it has been observed that hyperthyroidism is associated with an increase in glucose-6-phosphatase activity (22).

GLUCOSE-6-PHOSPHATE–GLYCOGEN INTERCONVERSION

In the conversion of glycogen to glucose-6-phosphate, two enzymes are involved: phosphorylase and phosphoglucomutase. A summary of the data on the effects of prolonged cold exposure on the activities of these enzymes is given in table 2.

In neither liver nor muscle tissue was there any effect of cold on total phosphorylase activity. Muscle tissue in general exhibited approximately 10 times the activity that liver did. This finding would be in agreement with the marked glycogenolytic capacity of the former tissue.

In view of the lack of a cold effect on total phosphorylase, the cold effect, if any, might possibly be reflected

TABLE 2. *Effect of Prolonged Cold Exposure on Liver and Muscle Phosphoglucomutase and Phosphorylase Activities*

Enzyme	Control			Cold-Exposed			Δ	t
	N	Mean*	S.E.	N	Mean*	S.E.		
Liver								
Phosphoglucomutase	10	34.06	±1.46	12	32.62	±1.68	−1.44	<1.0
Total Phosphorylase	9	7.55	±0.53	9	8.90	±0.96	+1.45	<1.0
Muscle								
Phosphoglucomutase	10	98.76	±4.58	11	101.22	±5.08	+2.46	<1.0
Total Phosphorylase	8	83.72	±3.12	8	94.38	±3.82	+10.66	2.24
Phosphorylase *a*	6	26.6	±1.52	4	28.9	±2.29	+2.3	<1.0
Phosphorylase *a* + *b*	6	45.9	±3.30	5	47.0	±3.68	+1.1	<1.0
Ratio $\frac{a}{a+b}$	6	0.58	±0.038	4	0.62	±0.035	+0.04	<1.0

P not significant. *Activities are expressed as μmoles of substrate converted per gm of original tissue per min.

in the levels of phosphorylase *a* (the active form) and phosphorylase *b* (the inactive form). In other words, the quantity of phosphorylase *a* may have been altered by cold exposure while the sum of phosphorylase *a* and *b* remained unaltered. A summary of the experiments on muscle tissue designed to answer this possibility is also shown in table 2 where the pertinent data to be considered are the ratios of phosphorylase *a* to the sum of phosphorylase *a* and *b*. Briefly, cold exposure had no effect on this ratio. One should note, however, that the total phosphorylase activity, that is, the sum of the *a* and *b* forms, is considerably lower in this assay system than in the previous one where total phosphorylase was assayed. The reason for this discrepancy is unknown.

Since in the initial steps of glycogen catabolism the rate limiting step seems to be phosphorylase (23), we were surprised to find no indication in either liver or muscle that cold exposure altered the specific activity of this enzyme. Our anticipation of a change in phosphorylase activity was based on two factors: *a*) the data indicating an increased sensitivity to the calorigenic action of epinephrine in the cold-acclimatized rat (19, 24), and *b*) evidence that epinephrine exerts its action at the phosphorylase level of glucose metabolism (23). In the latter instance, epinephrine was shown to act in the reconversion of the *b* form of phosphorylase to the *a* form.

Obviously the foregoing data do not support the thesis that the augmented thermogenesis in the cold-acclimatized rat is facilitated by epinephrine acting at the phosphorylase level of glycolysis; however, it does not rule out the possibility that epinephrine may be acting elsewhere.

Both liver and muscle phosphoglucomutase, like phosphorylase, were little affected by cold exposure. In the case of phosphoglucomutase, the lack of a cold effect was not too unexpected in view of the extremely high specific activity of this component in the glycolytic chain of enzymes. This finding would be in agreement with evidence (23) that the initial steps in the breakdown of glycogen are not limited by phosphoglucomutase activity. Comparing enzyme activities between tissues one will observe that muscle tissue has approximately three times the phosphoglucomutase activity of liver tissue. One would expect this from the marked glycogenolytic activity of the former tissue. In fact, insofar as muscle tissue is concerned, both total phosphorylase and phosphoglucomutase exhibit similar activity levels which would suggest that neither offers much hindrance to glycogenolysis. This finding is to be contrasted with liver tissue where total phosphorylase is only about one-fourth as active as phosphoglucomutase, thus suggesting that phosphorylase is a rate-limiting step. Sutherland arrived at similar conclusions in his work with liver slices (23).

In the conversion of glucose-6-phosphate to glycogen, two enzymes are the catalysts: phosphoglucomutase and uridine diphosphoglucose transferase. Of the two, only the activity of the phosphoglucomutase was assayed in these experiments, and as pointed out above, the extremely high activity of this component would indicate that it is not rate-limiting. What the effect of cold exposure would be on uridine diphosphoglucose transferase activity is unknown at present (see addendum).

HEXOSE-MONOPHOSPHATE SHUNT ACTIVITY

Evaluation of the effect of cold exposure on the activity levels of hexose-monophosphate shunt enzymes was made by assaying glucose-6-phosphate dehydrogenase, which in the initial step catalyzes the dehydrogenation of glucose-6-phosphate to form 6-phosphogluconate, and 6-phosphogluconate dehydrogenase, which in turn catalyzes the dehydrogenation and oxidative decarboxylation of 6-phosphogluconate to form ribulose-5-phosphate. In liver both of these enzymes exhibited significantly lower specific activities after cold exposure than before such exposure. Thus the cold-exposed group has only about one-half the glucose-6-phosphate dehydrogenase and about three-fourths the 6-phosphogluconic dehydrogenase activity shown by the controls. In these data it will be observed that the degree of reduction in activity wrought by cold exposure is more marked for glucose-6-phosphate dehydrogenase than for 6-phosphogluconic dehydrogenase.

The effect of cold exposure on the glucose-6-phosphate and 6-phosphogluconic dehydrogenase activity of muscle tissue was in the same direction as that observed in liver; i.e. both of these dehydrogenases exhibited reduced activities following cold exposure (table 3). The markedly lower general activity of these enzymes in muscle compared with liver would indicate the hexose-monophosphate shunt is not nearly as active in muscle as in liver. In addition, the relative effect of cold on the

TABLE 3. *Effect of Prolonged Cold Exposure on Liver and Muscle Glucose-6-Phosphate and 6-Phosphogluconic Dehydrogenase*

Enzyme	Control			Cold-Exposed			Δ	t
	N	Mean*	S.E.	N	Mean*	S.E.		
Liver								
G-6-P Dehydrogenase	5	4.66	±0.110	5	2.20	±0.130	−2.46	14.77
6-P-G Dehydrogenase	5	18.48	±1.096	5	13.18	±0.652	−5.30	4.15
Muscle								
G-6-P Dehydrogenase	5	0.330	±0.0106	5	0.266	±0.0152	−0.064	3.44
6-P-G Dehydrogenase	5	0.924	±0.018	5	0.760	±0.040	−0.164	3.68

$P < 0.01$. *Activities are expressed as μmoles of substrate converted per gm of original tissue per min.

TABLE 4. *Effect of Prolonged Cold Exposure on the Terminal Span of Glycolytic Enzymes Leading to Pyruvate Formation*

Substrate	Control			Cold-Exposed			Δ	t
	N	Mean*	S.E.	N	Mean*	S.E.		
None	5	0.26	±0.015	5	0.48	±0.021	+0.22	8.46
3-Phosphoglycerate	5	6.96	±0.472	5	10.52	±0.351	+3.56	6.04

$P < 0.01$. *Activities expressed in μmoles of pyruvate formed per gm of original tissue per min.

enzymes of the shunt is not nearly as great in muscle as it is in liver. For example, glucose-6-phosphate dehydrogenase activity was reduced to about one-half in liver but only to about four-fifths in muscle tissue as a result of cold exposure.

The marked lowering of glucose-6-phosphate dehydrogenase and 6-phosphogluconic dehydrogenase would suggest that hexose-monophosphate shunt activity is depressed during prolonged cold exposure. In contrast to this, Smith and Fairhurst (25), in measurements on these same enzymes, observed no effect with long-term cold exposure. Masoro *et al.* (6) reported no change in the relative rates at which glucose-1-C^{14} and glucose-6-C^{14} form CO_2. The apparent discrepancy between the present data and these reports, however, may merely reflect differences due to cold-exposure intervals. Both of the cited reports involved much longer exposure intervals than those used here—a factor that has been shown (26) to exert a strong influence on tissue oxidation rates.

One thing the data on the glucose-6-phosphate and 6-phosphogluconic dehydrogenases do indicate is that the 1-month cold-exposed animal has a markedly decreased capacity to reduce TPN. Since evidence has been presented in the literature (27) to indicate that glycolytic TPN reduction is coupled to fatty acid synthesis, a lowered activity on the part of these dehydrogenases could well be responsible for the depressed fatty acid synthesis observed in the cold-acclimatized rat (6, 28).

The reduction in the activity of these two dehydrogenases probably is not an effect of high thyroid activity in the cold. On the contrary, it has been shown (22) that hyperthyroidism leads to just the opposite result, i.e. increased glucose-6-phosphate and 6-phosphogluconate dehydrogenase activities. As far as could be determined from the literature, no other hormone can be implicated in the reduction of glucose-6-phosphate and 6-phosphogluconate dehydrogenase activities. On prolonged administration, most of the hormones studied have either no effect or a stimulatory one on these enzyme activities. The only experimental condition where we have observed a decline similar to that seen in cold-exposed animals has been in rats fed very high fat diets (unpublished observations).

TERMINAL GLYCOLYTIC ACTIVITY

Up to this point, all of the experiments have been concerned with enzymes operating at the hexose level in the glycolytic system. To obtain information on the effect of cold on the terminal stages of glycolysis, two additional assays were conducted in liver tissue (table 4). The first of these was the endogenous rate of pyruvate formation by soluble enzymes, and the second was the formation of pyruvate from 3-phosphoglycerate. The latter was used as a measure of the over-all activity of the reactions catalyzed by phosphoglyceromutase, enolase and pyruvic kinase.

Both of these assays exhibited considerably more activity in the tissue from the cold-exposed group than in the tissue from the control group, the rate being about doubled in the endogenous measurements and increased by about 50% in the 3-phosphoglycerate measurements (table 4).

The cold-induced increase in the activity of both muscle and liver glucokinase, together with the increase in the activity of the enzymatic components associated with the terminal stages of glycolysis, seems to indicate an augmented capacity to catabolize glucose to at least the pyruvate level. Since the enzyme systems of the aerobic phase of metabolism are much more active in the cold-acclimatized animal (7, 8), presumably the pyruvate, once formed, could readily be converted to CO_2 and H_2O. One should keep in mind, however, that the activity of the pyruvic oxidase system has not been assayed in the cold-acclimatized animal. To be more specific, the gaps in our knowledge are limited to two possible steps: one is the conversion of pyruvate to malate by way of malic enzyme; the other is the conversion of pyruvate to acetate (acetyl-Co A). The latter

compound has been shown (28) to be oxidized at greater rates in liver tissue from 10-day cold-acclimatized rats.

Viewed from the reverse direction, the increased activity in the terminal glycolytic system seems to indicate that at least part of the mechanism behind the enhanced ability of the fasting, cold-acclimatized rat is the maintenance of liver glycogen and blood sugar levels (3, 5). These data, together with the increased activity of glucose-6-phosphatase, show that the liver of the cold-acclimatized rat has an increased gluconeogenic capacity and hence would be better able to maintain blood sugar levels in the face of a restricted glucose intake, e.g. in fasting. However, one should note that these data do not rule out the possibility that there may be a 'sparing' of carbohydrate in the fasted, cold-acclimated animals. Evidence favoring this latter alternative is seen in the elevated rates of acetate (28), β-hydroxybutyrate, and glutamate (7) oxidation in the livers of the cold-acclimatized rats.

ADDENDUM

As correctly pointed out by Dr. Morales in the discussion of the results obtained in these experiments, little can be said regarding the effect of cold on the conversion of glucose-1-phosphate to glycogen. Phosphorylase, as he has indicated, is apparently not involved in this conversion, the equilibrium being in favor of glucose-1-phosphate. Rather, as shown by Leloir and Cardini (29), the synthesis of glycogen proceeds via uridine diphosphoglucose transferase. The effect of cold on the activity of this enzyme has yet to be assayed.

Another factor that has arisen since these experiments were conducted concerns the role of pyridoxyl-5-phosphate as a coenzyme for phosphorylase. This was demonstrated recently in Cori's laboratory (30). Whether prolonged cold exposure has any effect on phosphorylase via this route has not been determined.

REFERENCES

1. Pagé, E., L. M. Bavineau and J. P. Lachange. *Rev. Can. Biol.* 14: 144, 1955.
2. Wertheimer, E. and V. Bentor. *Gerentologia* 1: 306, 1957.
3. Hannon, J. P. and D. W. Young. *Am. J. Physiol.* 197: 1008, 1959.
4. Masoro, E. J. and J. M. Felts. *Fed. Proc.* 18: 99, 1959.
5. Pagé, E. and L. M. Babineau. *Canad. J. Biochem. & Physiol.* 32: 395, 1954.
6. Masoro, E. J., J. M. Felts and S. S. Panago. *Am. J. Physiol.* 189: 479, 1957.
7. Hannon, J. P. *Proc. Soc. Exper. Biol. & Med.* 97: 368, 1958.
8. Hannon, J. P. *Am. J. Physiol.* 198: 740, 1960.
9. Hsieh, A. C. and L. D. Carlson. *Am. J. Physiol.* 190: 243, 1957.
10. Depocas, T. G., G. K. MacLeod and J. S. Hart. *Rev. Can. Biol.* 16: 83, 1957.
11. Spiegelman, S. *Cold Spring Harbor Symposia Quant. Biol.* 11: 256, 1946.
12. Spiegelman, S. and R. Dunn. *J. Gen. Physiol.* 31: 153, 1947.
13. Hannon, J. P. and D. A. Vaughan. *Am. J. Physiol.* 198: 375, 1960.
14. Stoesz, P. A. and G. A. LePage. *J. Biol. Chem.* 180: 587, 1949.
15. Rothstein, A. *Protoplasmatologia* 2E IV: 1, 1954.
16. Crane, R. K., and A. Sols. *J. Biol. Chem.* 203: 273, 1953.
17. Jervall, K. F., E. Walaas and O. Walaas. *Acta physiol. scandinav.* 35: 321, 1956.
18. Crane, R. K. and A. Sols. *J. Biol. Chem.* 206: 925, 1954.
19. Baker, D. G. and E. A. Sellers. *Am. J. Physiol.* 174: 459, 1953.
20. Wertheimer, E. and V. Bentor. *Exper. Med. & Surg.* 8: 378, 1950.
21. Hannon, J. P. *Am. J. Physiol.* 196: 890, 1959.
22. Glock, G. E., P. McLean and J. K. Whitehead. *Biochem. J.* 63: 520, 1956.
23. Sutherland, E. W. In: *Phosphorous Metabolism*, edited by W. D. McElroy and B. Glass. Baltimore: Johns Hopkins Press, 1952, vol. II, p. 577.
24. Swanson, H. E. *Endocrinology* 60: 205, 1957.
25. Smith, R. E. and A. S. Fairhurst. *Proc. Natl. Acad. Sci. U.S.* 44: 705, 1958.
26. Hannon, J. P. *Am. J. Physiol.* 192: 253, 1958.
27. Siperstein, M. D. and V. M. Fagan. *J. Clin. Invest.* 37: 1158, 1958.
28. Masoro, E. J., A. L. Cohen and S. S. Panagos. *Am. J. Physiol.* 179: 451, 1954.
29. Leloir, L. F. and C. E. Cardini. *J. Am. Chem. Soc.* 27: 6340, 1957.
30. Cori, C. F. and B. Illingworth. *Proc. Natl. Acad. Sci. U.S.* 43: 547, 1957.

Glucose metabolism in warm- and cold-acclimated rats[1]

FLORENT DEPOCAS
Division of Applied Biology, National Research Council, Ottawa, Canada

DEPOCAS, FLORENT. *Glucose metabolism in warm- and cold-acclimated rats.* Fed. Proc. 19, Suppl. 5: 106–109. 1960.—Alterations in carbohydrate metabolism observed in warm- and cold-acclimated animals are reviewed, and recent work on the dynamics of glucose metabolism in warm- and cold-acclimated white rats exposed to warm and cold environments is described.

THE PRESENT DISCUSSION WILL DEAL with cold exposure and cold acclimation from the point of view of those resultant biochemical changes which can be observed in intact animals.

Kayser (1, 2) concluded from respiratory quotient measurements that lipids are the foodstuff preferentially utilized for the 'thermogénèse de réchauffement.' Significant decreases in respiratory quotients were observed in fasted normal as well as fasted cold-acclimated rats when they were transferred from a warm to a cold environment (3). However, the R.Q. values were similar in the two groups of animals while actually exposed to cold, and differences attributed to acclimation were observed only when the measurements were made at 30°C; the cold-acclimated rats then had the lower R.Q. Administration of maltose led to a greater rise in R.Q. in the cold-acclimated rats. These authors concluded that rats acclimated to cold "oxidize fats preferentially" and that in these animals "the conversion of sugar to fat is increased." Further work by Pagé *et al.* (4, 5) showed that the rate of intestinal glucose absorption was increased in animals acclimated to cold, but that R.Q. studies could not indicate whether the extra sugar absorbed was oxidized or transformed into fats.

Other quantitative modifications of glucose metabolism can be observed in the cold-acclimated animal. A decreased glycogen content of heart, liver, diaphragm and perirenal fat, but no change in the skeletal muscle glycogen and in the blood glucose level of rats were observed after a 2-hour fast following exposure for 45 days to 1.5°C (6). Hyperglycemia occurs in rats fasted for 24 hours following exposure to about 5°C for 9 days (7). Cold-exposed rats show increased sensitivity to insulin (6, 7). Finally, one may cite work showing a faster rate of disappearance of liver glycogen in cold-exposed, cold-acclimated rabbits (8) as evidence of participation of glucose in the metabolic response to cold.

It would be difficult to devise a unified pattern embodying these diverse observations indicating specific biochemical alterations related to the process of acclimatization to a cold environment, or for that matter simply to the response to cold exposure. In an effort to delve more deeply into the biochemistry of exposure and acclimation to cold while still keeping in mind the more or less intact animal, studies on glucose metabolism in cold-exposed and acclimated white rats were initiated in this laboratory a few years ago.

We found that the pattern of respiratory $C^{14}O_2$ production after intraperitoneal injection of glucose uniformly labeled with C^{14} (U-C^{14}-glucose) into rats at −5°C depended on the acclimation temperature of the animals. In the first intervals after injection of the U-C^{14}-glucose, cold-acclimated rats exhaled a larger proportion of the injected C^{14} as CO_2 than did the warm-acclimated rats. After 30 minutes, however, the warm-acclimated rats increased their $C^{14}O_2$ output above that of the 6°C rats, so that after 2.5 hours the 30°C rats had actually oxidized a larger percentage of the injected glucose. Warm- and cold-acclimated rats absorbed glucose from the peritoneal cavity at the same rate. Cold-acclimated rats exhaled intraperitoneally injected $HC^{14}O_3^-$ as CO_2 at a slightly higher rate than did warm-acclimated rats; however, the cumulative proportion of the injected C^{14} exhaled as CO_2 in 2 hours was similar in both groups of rats. Fat-free materials isolated from the carcasses of the 6°C rats given U-C^{14}-glucose contained more C^{14} than those of the 30°C rats, this fraction nearly accounting for the final group differences in cumulative $C^{14}O_2$ production (8a). These observations were interpreted as indicating greater interconversion of glucose and protein as well as faster rate of oxidation of glucose to CO_2 in the cold-acclimated rat (9).

When U-C^{14}-glucose was injected intravenously into anesthetized warm- or cold-acclimated rats at 30°C, and these were later transferred to an environment at 6°C, a significant increase in blood clearance of U-C^{14}-glucose occurred only in the warm-acclimated rats (10). Techniques permitting measurement of specific activity of plasma glucose in successive small samples of plasma from a single rat were developed for this work.

Experiments involving single injections of isotopically labeled substances result in continuously varying spe-

[1] Contribution from the Division of Applied Biology, National Research Council, Ottawa, Canada; issued as N.R.C. No. 5977.

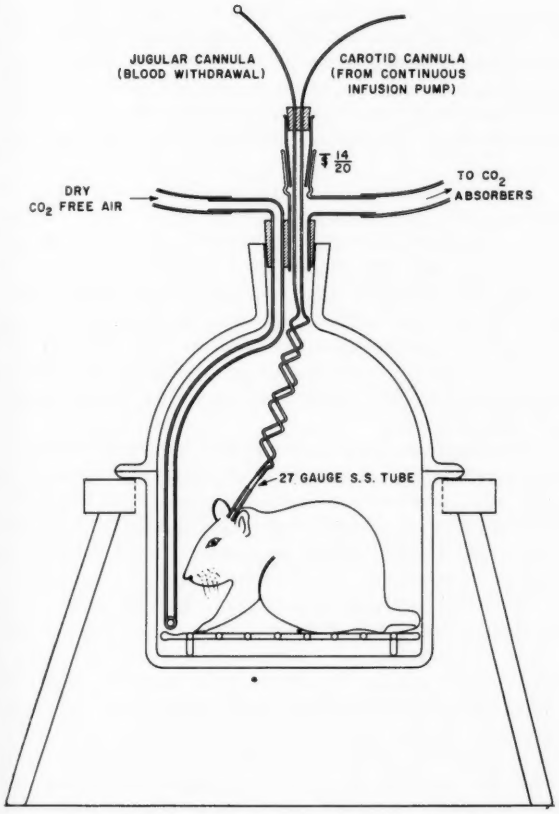


FIG. 1. Metabolism cage with rat in place for continuous infusion experiments.

cific activity of precursors and products and frequently yield data which, to say the least, are difficult to interpret. This is especially true with regard to the estimation of rates of synthesis and breakdown (11, 12). Our efforts were therefore directed towards the application to our problems of the elegant methods developed by Searle, Strisower and Chaikoff (13, 14). These allowed measuring, in the dog, the pool size and distribution space of body glucose as well as its rates of turnover and oxidation. This was done by maintaining the specific activity of the circulating glucose at a constant value.

Applying these techniques to the anesthetized rat in a 30°C environment, we found significant differences between warm- and cold-acclimated animals in only one parameter of glucose metabolism, namely glucose space; this was larger in the 6°C acclimated rats (15). Although the anesthetized rat reacts to cold exposure by an increase in oxygen consumption (16), its body temperature falls so rapidly in the cold that a study of alterations in carbohydrate metabolism associated with cold exposure cannot be conducted under even approximately steady-state conditions in this preparation. Work on this problem had to await recent development of a cannulation technique which allows infusion of materials and blood withdrawal in unrestrained, unanesthetized rats (17). This technique was easily extended to allow infusion and blood sampling from a rat enclosed in a metabolism chamber (fig. 1) and was used to measure directly the contribution of glucose as a substrate for cold-induced thermogenesis in warm- and in cold-acclimated rats (18). This made it possible to verify that cold thermogenesis involves an increase in glucose turnover in warm-acclimated rats, and allowed us to determine whether or not cold exposure involves an increase in the rate of oxidation of glucose in warm- and in cold-acclimated rats. If cold thermogenesis were strictly dependent upon fat oxidation, the rate of oxidation of glucose ought not to be increased at all under these conditions.

In a pilot experiment, the turnover time of plasma glucose was measured by following the decline in specific activity of plasma glucose in rats given a single injection of a trace amount of U-C^{14}-glucose (table 1). These measurements then allowed setting up the continuous infusion procedure in such fashion that constant specific activity of plasma glucose, as well as of the respiratory CO_2, was maintained.

The size of the pool of body glucose did not differ significantly in any of the four groups of rats; if it averaged approximately 19 mg glucose carbon/100 gm body weight.

Table 2 shows that exposure of the warm-acclimated rats to an environment at 6°C provoked an increase in the rate of glucose turnover. As measured by the technique of continuous infusion of U-C^{14}-glucose into non-fasted rats, the turnover rate of glucose is the result of three processes which take place simultaneously: *1*) absorption of glucose from the intestine (with consequent storage in the liver or utilization by the peripheral tissues), *2*) outflow of glucose from the liver to the peripheral tissues, and *3*) removal by the liver of labeled glucose in the circulation and its replacement with unlabeled glucose (19). This last process, the importance of which is unknown, would be expected to occur even when the first process is negligible. An increase in the rate of turnover of plasma glucose in animals exposed to cold could involve an increase in any one or in all of the enumerated processes. The rate of intestinal absorption of glucose would not be expected to be dependent on short-term exposures to cold environments, although this possibility cannot be ruled out at this time. The observed increase in glucose turnover rate could not be accounted for by uptake of labeled glucose by the liver with release of unlabeled glucose, because the specific activities of glycogen terminally isolated from the livers were not significantly different in the two groups of rats. The increase in turnover rate of glucose in the warm-acclimated rats is best explained on the basis of an accelerated rate of glucose transfer from the liver to the peripheral tissues. These observations on unanesthetized, cannulated rats are in agreement with previous observations showing a faster clearance of U-C^{14}-glucose from the plasma of anesthetized, warm-acclimated rats when transferred from a warm to a cold environment (10).

XUM

TABLE 1. *Turnover Times of Plasma Glucose (U-C^{14})* in Unanesthetized Acclimated Rats*

Acclimation Temperature	Mean Turnover Times (*min.*) and S.E.		Diff.
	at 30°C	at 6°	
30°C	55.1±4.4	39.9±4.4	15.2±6.2†
6°C	48.3±4.4	41.3±4.4	6.9±6.2
Diff.	6.8±6.2	1.4±6.2	

* Single injection of U-C^{14}-glucose (3 animals in each group).
† Difference significant at 5% level.

TABLE 2. *Average Respiratory CO_2 Production and Rates of Turnover and Oxidation of Glucose in Unanesthetized 30° and 6°C Acclimated Rats Exposed to 30° and 6°C*

Treatment Group	Respiratory CO_2	Turnover Rate	Oxidation Rate	Ratio of Oxidation Rate: Turnover Rate	% Respiratory CO_2 Derived from Glucose Oxidation
	mg C/min. per b. wt.$^{0.6}$ × 10²			%	
			30°C rats		
30° to 30°C	7.36	3.05	1.48	48.5	20.1
30° to 6°C	13.26	4.85	2.91	60.0	21.8
			6°C rats		
6° to 30°C	8.87	4.12	1.99	48.6	22.5
6° to 6°C	15.53	5.27	3.08	58.0	19.7
(30° to 6°) − (30° to 30°)	5.90*	1.80*	1.43*	79.5†	24.3†
(6° to 6°) − (6° to 30°)	6.66*	1.15‡	1.09‡	95.0†	16.4†

* Significant to the 1% level. † These values refer to the extra turnover and oxidation rates of glucose and to the extra respiratory CO_2 of the rats at 6°C. ‡ Significant to the 5% level.

Exposure of the warm-acclimated rats to the cold environment also was associated with an increase in the rate of oxidation of body glucose; this increase in turn was proportionate to the increase in total CO_2 production. However, a significantly greater proportion of the glucose carbon flowing through the pool appeared as CO_2; the increase in plasma glucose turnover rate thus was not commensurate with the increase in CO_2 production in the cold. In the warm environment, 48.5% of the glucose turning over was oxidized via direct pathways; in the cold this was increased to 60%, the difference being statistically significant. These measurements indicate clearly that when an organism is faced with a new situation, in this case increased caloric output, readjustments can occur in the proportions of a specific substrate following each of several different alternative pathways of metabolism.

The changes described above for the warm-acclimated rats took place without significant alteration in the proportion of exhaled CO_2 derived from glucose oxidation; this averaged 20.1% in the warm and 21.8% in the cold environment. Part of the extra heat was produced by increasing oxidation of glucose in almost exactly the same proportion as total CO_2 production. This observation implies that the major part of the extra heat production of the cold-exposed animals was obtained from non-carbohydrate reserves, most likely from lipids. Since heat production of warm-acclimated rats in the cold is considered to be almost entirely due to shivering, this finding is in accord with current work on muscle metabolism indicating that the classical emphasis on preferential carbohydrate utilization by muscle is not justified (20, 21).

Essentially the same changes in reverse were seen when the cold-acclimated rats were transferred from 6°C to 30°C. Production of CO_2, rates of turnover and oxidation of glucose, and proportion of glucose turning over which was promptly oxidized were all decreased (table 2). The decrease in oxidation rate, however, accounted for 95% of the decrease in turnover rate. These readjustments also took place without any significant alteration in the proportion of respiratory CO_2 derived from glucose oxidation.

The significant decrease in rate of glucose turnover in nonanesthetized, cold-acclimated rats on transfer from a cold to a warm environment is apparently not in accord with the lack of increase of glucose clearance in anesthetized, cold-acclimated rats transferred from a warm to a cold environment as described previously (10); similarly, such a result would seem to conflict with the absence of a significant increase in turnover time of plasma glucose when nonanesthetized, cold-acclimated rats are transferred from a cold to a warm environment (table 1). Since turnover rate is the ratio of pool size to turnover time, significant alterations in turnover rate should be associated with similar alterations in turnover time if the pool size remained constant. A possible explanation for the apparent conflict between these results is the fact that the change in glucose turnover rate is considerably smaller when cold-acclimated rats are transferred to a warm environment than when warm-acclimated rats are transferred to the cold room. The more accurate estimation of turnover rate by continuous infusion of U-C^{14}-glucose then might well reveal significant changes where the less accurate measurements of turnover time obtained by the single dose method would fail to detect them.

Differences in the rates of turnover and oxidation of glucose related to temperature of acclimation were seen only in the unanesthetized rats tested in a 30°C environment where these values were higher in the 6°C acclimated rats (table 2). No such differences were observed when similar measurements were performed in anesthetized rats (15). The interpretation of differences in absolute rates of turnover and oxidation of glucose is difficult because these values very likely are dependent on the food intake of the animals in the immediate past. In this respect, it can also be pointed out that although warm- and cold-acclimated rats showed the same glucose turnover and oxidation rates when tested in an environment at 6°C, the mechanisms acting to produce and maintain these high rates could well be different. A study of glucose metabolism in fasted animals might clarify the situation.

Work on the more biochemical aspects of acclimation to cold has not yet led to observation of such striking differences as are observed on a more physiological plane, such as decrease in shivering or increase in sensitivity to noradrenaline during acclimation of a white rat to cold. It would be difficult, however, to accept the conclusion that such fundamental changes are not associated with profound alterations in the biochemistry of control of heat production and substrate availability at the cellular level. Many of these readjustments remain to be elucidated.

REFERENCES

1. KAYSER, C. *Compt. rend. soc. biol.* 126: 701, 1937.
2. KAYSER, C. *Compt. rend. soc. biol.* 126: 1219, 1937.
3. PAGÉ, E. AND L. P. CHÉNIER. *Rev. Can. Biol.* 12: 530, 1953.
4. PAGÉ, E. AND L. M. BABINEAU. *Can. J. Biochem. & Physiol.* 32: 395, 1954.
5. PAGÉ, E., L. M. BABINEAU AND J. P. LACHANCE. *Rev. Can. Biol.* 14: 144, 1955.
6. BAKER, D. G. AND E. A. SELLERS. *Am. J. Physiol.* 174: 459, 1953.
7. MANSOUR, T. E. AND W. F. HEWITT, JR. *Endocrinology* 54: 20, 1954.
8. OGLE, C. AND C. A. MILLS. *Am. J. Physiol.* 103: 606, 1933.
8a. DEPOCAS, F., G. K. MACLEOD AND J. S. HART. *Rev. Can. Biol.* 16: 83, 1957.
9. POTTER, V. R. *Fed. Proc.* 17: 1060, 1958.
10. DEPOCAS, F. *Can. J. Biochem. & Physiol.* 37: 175, 1959.
11. REINER, J. M. *Arch. Biochem. and Biophys.* 46: 53, 1953.
12. RUSSELL, J. A. *Perspectives in Biochem. and Med.* 1: 138, 1958.
13. SEARLE, G. L., E. H. STRISOWER AND I. L. CHAIKOFF. *Am. J. Physiol.* 185: 589, 1956.
14. SEARLE, G. L., E. H. STRISOWER AND I. L. CHAIKOFF. *Am. J. Physiol.* 176: 190, 1954.
15. DEPOCAS, F. *Can. J. Biochem. & Physiol.* 37: 285, 1959.
16. HEROUX, O., J. S. HART AND F. DEPOCAS. *J. Appl. Physiol.* 9: 399, 1956.
17. POPOVIC, V. AND P. POPOVIC. *J. Appl. Physiol.* 15: 727, 1960.
18. DEPOCAS, F. AND R. MASIRONI. *Am. J. Physiol.* In press.
19. STEELE, R., J. S. WALL, R. C. DE BODO AND N. ALTSZULER. *Am. J. Physiol.* 187: 15, 1956.
20. INGLE, D. J., E. H. MORLEY AND D. STETTEN, JR. *Am. J. Physiol.* 182: 263, 1955.
21. FRITZ, I. B., D. G. DAVIS, R. H. HOLTROP AND H. DUNDEE. *Am. J. Physiol.* 194: 379, 1958.

Cold exposure and the immune response[1]

IGNATIUS L. TRAPANI[2]

Division of Chemistry and Chemical Engineering, the California Institute of Technology, Pasadena, California[3]

TRAPANI, IGNATIUS L. *Cold exposure and the immune response.* Fed. Proc. 19, Suppl. 5: 109–114. 1960.—Protein metabolism in the cold-exposed rabbit has been studied mainly through the use of immunological techniques, free-boundary electrophoretic analyses of the plasma proteins, and alterations in whole blood and plasma clotting times. Active and passive immunization in surgically thyroidectomized and thyroxin-treated rabbits not exposed to cold was also investigated, since similar experiments in rabbits exposed to an environmental temperature of −15°C suggested the possibility that thyroid activity might play a role in the immune response of the cold-exposed animal.

AS THE PARTICIPANT RESPONSIBLE for a discussion of protein metabolism in animals exposed to low environmental temperatures, I may disappoint some of the audience by not presenting a short review of protein metabolism, either in the general sense or relative to the cold-exposed animal. In the first instance, the subject matter would be too extensive and in the second, there is little previous work pertinent to this topic except for a few reports relating to nitrogen excretion in the cold-exposed animal. I hope that my discussion today will add something of value to our concepts of the alterations which take place in the chronically cold-exposed animal and may lead to further studies of protein metabolism under such an environmental stress.

During the past 4 years an investigation has been underway, with the collaboration of Professor Dan H. Campbell and Dr. G. B. Sutherland, on the alterations in the immune response and the circulating components of the blood in animals exposed to low environmental temperatures (1–3; and Trapani and Campbell, unpublished observations). This avenue of approach to the study of protein metabolism has been mainly through the use of immunological techniques and free-boundary electrophoretic analyses of the plasma proteins.

[1] This work has been supported by the Office of Naval Research under Contract NR 102-392.

[2] Present address: Department of Experimental Immunology, Research Institute, National Jewish Hospital, Denver, Colo.

[3] Contribution No. 2518.

CHANGES IN THE CIRCULATING PLASMA PROTEINS AND FORMED ELEMENTS OF RABBIT BLOOD

In these experiments, five groups of healthy male rabbits weighing between 2.5 and 3.0 kg were used. The controls were kept at room temperature, 20°–25°C (69°–77°F), and the cold-exposed groups were treated as follows:

Group 1. These animals were maintained at 4°C (39°F) for one week. They were clipped of all hair, except on the head and extremities, before exposure.

Group 2. These animals were maintained at 4°C for 8 weeks. The hair was progressively removed from all parts of the body, except the head and extremities, during the first month, and the animals were maintained thus during the remainder of the period. These animals and those of *group 1* were kept on shavings in individual cages in a walk-in cold room of about 350 cubic foot capacity.

Groups 3 and 4. The animals in these groups were maintained at −15°C (5°F) for 10 weeks, in a specially designed cold box with a capacity of 10 rabbits. Adequate provision was made for lighting and fresh air without drafts, and the animals were kept on wire mesh in individual cages. Water was changed four times a day because of freezing and standard food was provided ad libitum. The animals of *group 3* were not clipped, while those of *group 4* were clipped during the 2nd month (as in *group 2*) and were maintained thus for the remainder of the exposure period. Rabbits clipped to this extent before exposure died within a few hours at −15°C. The rectal temperatures of the animals kept at −15°C were obtained by means of a Foxboro Dynalog apparatus equipped with resistance thermometers. The temperatures were taken several times over the 10-week period in order to accustom the animals to this maneuver. Rectal temperatures in degrees centigrade of the two groups were: *group 3* 39.04° ± 0.54° and *group 4* 38.87° ± 0.44°, while that of the room temperature controls was 39.50° ± 0.17°.

The data in the first two tables are presented not only as the means of the original values but also as a percentage of their own control values.

Table 1 presents the values for certain hematological parameters in the cold-exposed rabbit. There are increases in the platelet and erythrocyte counts, hematocrit and total plasma protein concentration. An exception appears in the platelet count of *group 3*, the animals maintained at −15°C with their pelage intact. This group will be discussed later.

In table 2 are shown the results of the clotting studies. Whole blood and plasma clotting times increase, as does the fibrin yield, while there is a decrease in prothrombin time. In the columns under plasma clotting times, *Sample A* refers to platelet-containing plasma, while *Sample B* refers to platelet-poor plasma.

Table 3 displays the results of the free-boundary electrophoretic analyses of the plasma of the cold-exposed rabbits. These were made with the Perkin-Elmer apparatus using pH 8.6 veronal buffer, ionic strength 0.1. The electrophoretic analyses demonstrate a change in the percentage composition of plasma as a result of cold adaption, but no change in mobility. There is a decrease in the relative concentration of the faster moving components, albumin and α-globulin, and an increase in the slower components, β-globulin and fibrinogen. The γ-globulin results are not consistent and may be a reflection of the differences in the conditions of the cold exposure; γ-globulin is increased in *groups 1* and *2*, and decreased in *groups 3* and *4*.

The onset of the response to cold exposure appears to occur very early, i.e. in 1 week or less. Platelet and plasma protein changes are well underway in this short time, although the erythrocyte changes have not yet appeared. It is interesting that the alterations which occur in unclipped animals after 10 weeks at −15°C (*group 3*) were relatively minor, indicating that these animals may not have been severely stressed, even at this low temperature. The reason for this may have been a more adequate adjustment of the insulating properties in this group of animals, with the development of an essentially normal microenvironment. They might thus avoid the necessity for the other changes in the more severely stressed (clipped) groups. In a situation in which the insulating capacity of the body surface has been increased no further cold adaption might take place, or perhaps there could even occur a reversal of cold adaptation if the improvement in the insulating capacity were to exceed the requirements of the environmental stress. In this regard then, it is possible that this unclipped group of animals may not have been physiologically cold adapted.

In reference to the clotting studies, the decrease in prothrombin time is in part the result of increased fibrinogen; the longer whole blood and plasma clotting times seem to be the result of a decreased efficiency of the thromboplastic mechanism, since there appears to be an inverse relationship between prothrombin time and fibrinogen concentration (fig. 1). Factors other than fibrinogen concentration may be implicated even here since the considerable difference in this component between *groups 2* and *4* produced little change in prothrombin time.

The maximum response obtainable by cold exposure undoubtedly varies with time, temperature and the parameter studied. It must have been very nearly reached, if not indeed passed, by the clipped animals kept at −15°C. Under these conditions some of the variables studied appeared to have passed through a maximum and may have been returning to more normal values. The platelet count, for example, was highest in those animals which were subjected to cold (4°C) for the shortest time. These animals, however, had their hair removed before cold exposure and may have suffered more acute stress than the animals which were gradually clipped. Fibrinogen concentration, on the other hand, rose markedly between *groups 2* and *4*, and

TABLE 1. HEMATOLOGICAL CHANGES IN COLD-ADAPTED RABBITS

Group	Conditions	No.	Platelet Count*		Erythrocyte Count*		Hematocrit		Total Plasma Protein, gm/100 ml	
			Mean	Control, %	Mean	Control, %	Mean	Control, %	Mean	Control, %
1	Control	6	251		6194		41.1		5.87	
	1 wk., 4°C, clipped	6	342	136(.1)†	6171	100	41.1	100	6.01	102
2	Control	5	366		5570		41.9		7.25	
	8 wk., 4°C, clipped	6	416	114(.2)	5900	106(.3)	45.0	107(.05)	7.56	104(.2)
3	Control (for *groups 3* and *4*)	6	551		6370		41.4		5.44	
	10 wk., −15°C, unclipped	4	398	72(.2)	7208	113(.1)	47.7	112(.01)	6.02	113(.3)
4	Control (as in *group 3*)									
	10 wk., −15°C, clipped	3	641	116(.5)	6616	104(.7)	43.7	106(.4)	6.65	123(.01)

* ×1000. † Figures in parentheses are *P* values from Fisher's *t* test

TABLE 2. CLOTTING DATA ON BLOOD FROM NORMAL AND COLD-ADAPTED RABBITS

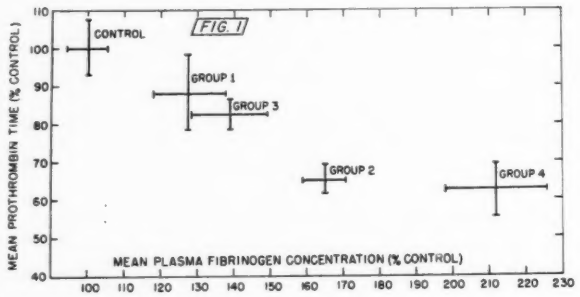
Group	Condition	No.	Clotting Times						Prothrombin Time, sec.		Fibrin Yield gm/100 ml plasma	
			Whole blood, min.		Plasma							
					A, sec.		B, sec.					
			Mean	Control, %	Mean	Control, %	Mean	Control, %	Mean	Control, %	Mean	Control, %
1	Control	6	14.9		79		116		48.5		0.32	
	1 wk., 4°C clipped	6	17.2	115(.4)*	79	100	123	138(.6)	42.5	88(.4)	0.41	127(.05)
2	Control	5	23.1		79		211		57.3		0.44	
	8 wk., 4°C, clipped	6	32.4	140(.1)	86	109(.4)	283	134(.5)	37.0	65(.01)	0.62	141(.01)
3	Control (for *groups 3* and *4*)	6	27.6		55		93		39.3		0.38	
	10 wk., −15°C, unclipped	4	30.2	109(.3)	53	95(.5)	78	84(.1)	32.3	82(.05)	0.42	112(.5)
4	Control (as in *group 3*)											
	10 wk., −15°C, clipped	3	38.4	139(.01)	67	122(.05)	108	113(.2)	24.5	62(.01)	0.73	194(.02)

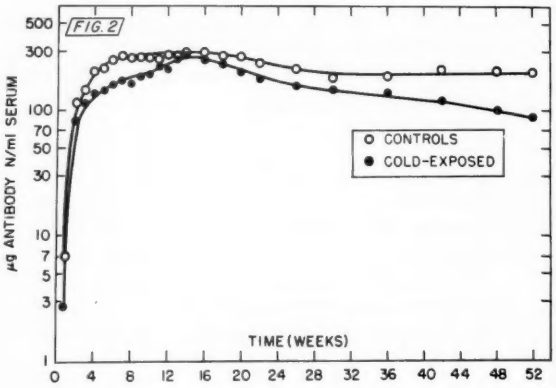
* Figures in parentheses are *P* values from Fisher's *t* test

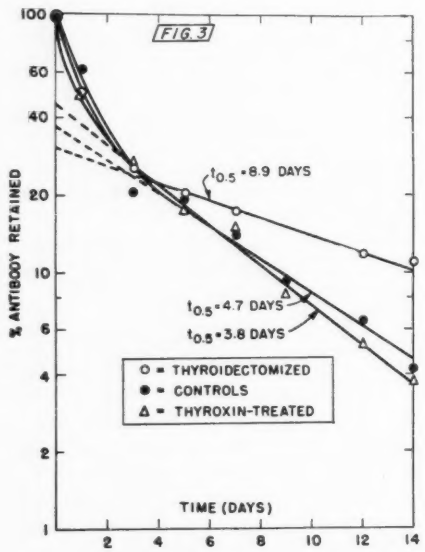
TABLE 3. ELECTROPHORETIC DISTRIBUTION OF PLASMA PROTEINS OF NORMAL AND COLD-ADAPTED RABBITS

Group	Condition	No.	Albumin		α Globulin		β Globulin		Fibrinogen		γ Globulin	
			Mean*	Control %	Mean	Control, %	Mean	Control, %	Mean	Control, %	Mean	Control, %
	Controls	10	66.0		9.5		10.0		8.2		5.9	
1	1 wk., 4°C, clipped	6	62.7	95(.1)†	8.5	89(.1)	11.7	117(.05)	10.3	125(.01)	7.1	121(.4)
2	8 wk., 4°C, clipped	5	57.4	87(.01)	8.1	85(.1)	14.2	142(.01)	13.0	158(.01)	7.3	125(.05)
3	10 wk., −15°C, unclipped	4	61.1	93(.2)	9.6	101	14.8	149(.01)	10.3	124(.2)	4.4	75(.1)
4	10 wk., −15°C, clipped	3	59.3	90(.02)	8.6	90(.4)	13.9	139(.01)	14.2	172(.02)	4.2	71(.02)

* % of total. † Figures in parentheses are *P* values from Fisher's *t* test







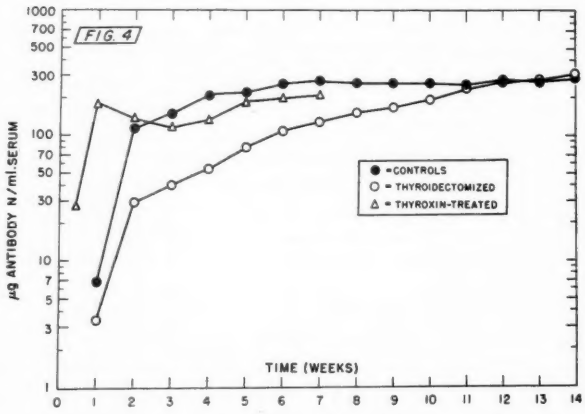


FIG. 1. Mean prothrombin time as a function of fibrinogen concentration in plasma from normal and cold-adapted rabbits. Group designations are defined in text.

FIG. 2. Circulating antibody levels in rabbits immunized with BSA plus Freund's adjuvant (10 mg BSA/kg b. wt.) at time zero. The cold-exposed group, kept at an environmental temperature of −15°C, was progressively clipped during the first 8 weeks and immunized after a 10-week exposure.

FIG. 3. Passive antibody decay in surgically thyroidectomized, thyroxin-treated, and untreated control rabbits.

FIG. 4. Circulating antibody levels in surgically thyroidectomized, thyroxin-treated, and untreated control rabbits immunized with BSA plus Freund's adjuvant (10 mg BSA/kg b.wt.) at time zero.

might be pushed even further with an increase in time or a decrease in temperature.

IMMUNE RESPONSE IN COLD-EXPOSED RABBITS

In these studies, rabbits were exposed to an environmental temperature of −15°C. After 2–3 weeks at this temperature the animals' hair was progressively clipped so that by the end of 8 weeks all hair except that on the head, extremities, and a 2-inch strip along the ventral surface had been removed. The rabbits were maintained in this clipped condition during the rest of the experimental period. The immunization studies were then made after the 10th week.

Passive antibody decay. Passive antibody decay studies have been used to assess the rate of protein turnover in the cold-exposed animal. The antibody used for these experiments was homologous gamma globulin (anti-bovine serum albumin (BSA)) prepared from high titer rabbit antiserum by precipitation with ammonium sulphate (⅓ saturation, pH 7.8). After two reprecipitations, the γ-globulin obtained was dissolved in pyrogen-free 1% NaCl. This preparation had a protein concentration of 2.75%, and migrated as a single symmetrical peak by free-boundary electrophoresis in barbital buffer (pH 8.6; $\mu = 0.1$). Twenty-five ml of this solution, containing 686 mg of protein, of which 197 mg was antibody protein, was injected intravenously into rabbits which had been kept at −15°C for 10 weeks, and also into rabbits kept at room temperature. The animals were bled periodically and the concentration of circulating antibody estimated by quantitative microprecipitin

analyses by a modification of the method of Lanni (4). The results were plotted semilogarithmically as the percentage of the injected dose remaining versus time. The slope of the linear portion of the curve (assumed to represent steady-state loss of antibody) was calculated by the method of least squares, extrapolated back to zero time, and the half-life values calculated from that point. Plasma protein concentrations were measured by digestion and direct nesslerization (4).

Since it is possible to use antibody as a tag for the estimation of what is taken to be analogous to plasma volume, antibody distribution space was measured by utilizing a sample obtained 10 minutes after the injection of homologous antibody in the passive antibody decay studies. It was assumed that the concentration of antibody in this sample was close to a zero-time extrapolation value. From the concentration of antibody in the 10-minute sample and the amount of antibody injected, the distribution volume was calculated and then corrected for the volume of antibody solution injected at time zero. The distribution volume of T-1824, measured by standard disappearance techniques, gave values consistent with those obtained by antibody dilution. Plasma protein concentrations of the pre-dye or pre-antibody samples were also measured. The results of passive antibody decay, plasma protein concentration, and the 'plasma volume' are summarized in table 4.

The data at hand indicate that protein turnover in the cold-exposed rabbit is more rapid than in room temperature controls. The increases which occur in total protein concentration, erythrocyte count and hematocrit support the suggestion that hemoconcentration occurs as a result of cold exposure. In addition, the indicated increase in plasma volume implies an increase in the total circulating blood volume. This must then represent an even more marked increase in the total mass of circulating protein and formed elements than is shown by the concentration studies. The increase in the plasma protein concentration which occurs as a result of the cold exposure does not necessarily produce an increase in the colloid osmotic (oncotic) effect of the plasma. The osmotic effect of the increase in total protein is offset by a reduction in the albumin: globulin ratio, so that the total oncotic pressure remains essentially constant.

Active antibody production. Rabbits exposed to −15°C for 10 weeks and clipped of hair as in previous experiments were actively immunized by the subcutaneous injection of bovine serum albumin (BSA) (10 mg/kg body weight) in Freund's adjuvant at time zero. The levels of circulating antibody, estimated by the quantitative precipitin analyses (4), were followed for a period of 52 weeks. Rabbits maintained at room temperature and treated in the same manner were used as controls. Figure 2 displays the results of this experiment. It should be noted that the logarithm of concentration of circulating antibody is plotted in this figure against time so that what may appear to be small differences in some areas of the curves may in reality be highly significant differences.

TABLE 4. *Plasma Protein Concentration, Plasma Volume, and Passive Antibody Decay in Rabbits*

	N	Plasma Protein *gm/100 ml*	PV *ml/kg*	Antibody Half Life *days*
Controls (18°C)	10	5.35±0.39*	49.5±6.1	4.7±0.2
Cold-exposed (−15°C)	7	7.19±0.66	58.3±4.3	3.4±0.2

* Standard deviation.

The level of circulating antibody in the cold-exposed group increases at a slower rate than in the control group and approaches control levels at approximately 14 weeks. Then there is a decline in both groups, but at different rates, throughout the remainder of the experimental period so that by the end of 52 weeks the level of circulating antibody in the cold-exposed animals is approximately 50% of that in the control group.

If we were to look only at these data, we might draw the conclusion that the cold-exposed animal does not synthesize antibody protein as well as the nonexposed animal. However, it must be remembered that curves of this type represent not only antibody production but also antibody decay. In the present case, a part of the difference, at least, may be attributable to an increase in protein degradation, as can be inferred from the passive antibody decay studies discussed above. Also, it is possible that there is a change in the rate of protein production itself, and further experiments are planned to shed light on this aspect.

INFLUENCE OF THE THYROID ON THE IMMUNE RESPONSE

One factor which may be implicated in the immune response of the cold-exposed animal is the role of the thyroid. In addition to the numerous observations of increased metabolic activity and thyroid activity in animals exposed to cold, there is an earlier report by Dixon (5) that passive antibody decay in thyroxin-treated rabbits is increased. In view of this, a study of passive and active immunization in rabbits which have been either surgically thyroidectomized or treated with thyroxin is in progress. I would like to discuss the data now available in the hope that such a presentation might clarify certain points of observation in our low-temperature experiments.

Rabbits weighing between 2.5 and 3.0 kg were thyroidectomized and allowed to recuperate for 2–3 weeks before being immunized. At this time their mean metabolic rate was approximately 75% of the control group. The surgical thyroidectomy was chosen in order to circumvent any possible direct effect of a goitrogen on the biochemical systems involved, which might mask the influence of the thyroid hormone. A second group of rabbits (2.5 to 3.0 kg body weight) were injected subcutaneously with 0.5 mg L-thyroxin on 3 successive days of the 1st week, then twice weekly thereafter. After

3 weeks their metabolic rate had stabilized at a level approximately twice that of the control group, and the animals were then immunized.

Figure 3 shows the time course for the decay of passively administered antibody (6). The half life of the antibody in the thyroidectomized rabbits is about twice as long (8.9 ± 0.4 days) as in the controls (4.7 ± 0.2 days), while in the thyroxin-treated rabbits the half-life of antibody is 3.8 ± 0.2 days.

Similarly prepared groups of rabbits were actively immunized with BSA in Freund's adjuvant as had been done previously with the cold-exposed rabbits. Figure 4 displays the data obtained so far which contain several points of interest.

The circulating antibody level in the thyroidectomized animals rises gradually and approximates the control level about 14 weeks after immunization. The thyroxin-treated group, on the other hand, not only has an initially higher level of circulating antibody, but also displays measurably increased amounts of antibody 3 days after immunization. This early response was not present in either of the other groups. After the initial high level of circulating antibody, there is a decline to levels below those of the controls, and then a second increase. Since this particular phase of the experiment is still in progress, the curve depicts only the data for the first 7 weeks.

DISCUSSION

The results of active and passive immunization under stress raise the question of whether a change in circulating antibody level is due primarily to an alteration in the antibody forming mechanisms or to the effect of these conditions on the mechanisms responsible for antibody decay.

If we consider the changes in antibody decay as being superimposed on an essentially normal rate of antibody production, the net result should be an apparent decrease in the immune response of the cold-exposed and the thyroxin-treated rabbits, and an apparent increase in the response of the thyroidectomized animals. If, on the other hand, there were also an alteration in the rate of antibody synthesis, the result would be either an accentuation of the immune response, if antibody production were affected in the opposite direction, or perhaps no observable difference if the change in antibody decay were offset by a change in antibody production in the same direction, that is, if the increase in antibody decay were compensated by an increased antibody production.

Since the thyroid studies were carried out under the a priori assumption that thyroid activity in the cold-exposed animal affected the immune response, it would be appropriate now to attempt to correlate the data obtained in the cold-exposed animals with those obtained in the thyroid studies.

First of all, passive antibody decay rates suggest that the increased thyroid activity of the cold-exposed animal is, at least in part, responsible for an increased protein turnover. The results obtained with active immunization, however, are certainly less clear. As a first approximation, the over-all response of the cold-exposed rabbit after active immunization is more like that of the hypothyroid animal than like that of the hyperthyroid animal. Protein turnover in the hypothyroid animal, however, is much slower than in the cold-exposed or the hyperthyroid animal. The gradual rise in circulating antibody in the hypothyroid animal can be the result of the increased half life of antibody superimposed on a normal, or less than normal, rate of antibody synthesis. In the cold-exposed animal, the increased rate of protein turnover would seem to be superimposed on a normal, or greater than normal, rate of antibody synthesis. The hyperthyroid animal appears to have a high initial rate of antibody synthesis which, even though coupled with an increased rate of protein turnover, leads to early high levels of circulating antibody, followed by a decline and then subsequent stabilization of the balance between the synthetic and catabolic mechanisms. A final point which should be mentioned is that the persistence of the antigen (7) and its degradation in the host animal may very well be altered under the conditions of study, and this in turn may have a considerable effect on antibody synthesis.

SUMMARY

The salient points derived from these studies which can be related to protein metabolism in the chronically cold-exposed animal are: changes in the electrophoretic distribution of the plasma proteins, an increase in the total mass of circulating protein, an increase in protein turnover, and an apparent decrease in the immune response. It is felt that the activity of the thyroid may exert some influence on these parameters in the cold-exposed animal. Since it is difficult to ascribe the changes in protein metabolism to cold exposure per se, it seems reasonable to attribute these alterations to the interplay of several factors including the hormonal alterations consequent to the stress of the cold exposure.

REFERENCES

1. Sutherland, G. B. and D. H. Campbell. *Proc. Soc. Exper. Med. & Biol.* 91: 64, 1956.
2. Sutherland, G. B., I. L. Trapani and D. H. Campbell. *J. Appl. Physiol.* 12: 367, 1958.
3. Trapani, I. L. and D. H. Campbell. *J. Appl. Physiol.* 14: 424, 1959.
4. Lanni, F., M. L. Dillon and J. W. Beard. *Proc. Soc. Exper. Med. & Biol.* 74: 4, 1950.
5. Dixon, F. J., D. W. Talmage, P. H. Mauer and M. Deichmiller. *J. Exper. Med.* 96: 313, 1952.
6. Trapani, I. L., A. Lein and D. H. Campbell. *Nature (London)* 183: 982, 1959.
7. Garvey, J. S. and D. H. Campbell. *J. Immunol.* 76: 36, 1956.

Alterations in hepatic lipid metabolism induced by acclimation to low environmental temperatures[1]

E. J. MASORO
Department of Physiology, Tufts University School of Medicine, Boston, Massachusetts

MASORO, E. J. *Alterations in hepatic lipid metabolism induced by acclimation to low environmental temperatures.* Fed. Proc. 19, Suppl. 5: 115–119. 1960.—Two distinct kinds of information have been made available by experimentation on hepatic metabolism in the cold-acclimated rat. First, insight has been gained concerning the acclimation process as it occurs at the molecular level of organization; a mechanistic explanation has been presented for two important phenomena: *a*) the great capacity of the cold-acclimated rat to resist fatty infiltration of the liver; *b*) the ability of the cold-acclimated rat to maintain liver glycogen at surprisingly high levels during fasting. Second, the cold-acclimated animal has been shown to be a powerful tool for studying the physiologic regulators of intermediary metabolism.

IN THE PROCESS OF ACCLIMATION to low environmental temperatures, the role of lipid metabolism is yet to be determined. For a fundamental understanding of its significance in this regard, it is not only necessary to know the details of lipid metabolism in the various tissues and organs of the body, but it is also essential to consider the interplay between these several tissues and organs in the total response of the organism. However, the fragmentary nature of the data available at this time does not permit attaining this ideal. Therefore this discussion will be limited to a description of the effects of cold acclimation on hepatic lipid metabolism. This choice of subject matter has been made for two reasons. First, the research activities of the speaker have been thus far primarily on liver metabolism. Second, very little data exist on the effects of cold acclimation on extrahepatic lipid metabolism—certainly not enough to permit one to present a coherent picture. However, I should like to warn against any tendency on the part of the audience to conclude that the findings on the liver are also probably true of the extrahepatic tissues. On the contrary, preliminary studies in our laboratory indicate that very few of the alterations noted for hepatic metabolism can be found in the metabolic activities of various extrahepatic tissues.

The primary research interest of our laboratory along these lines has been the investigation of the effects of acute cold exposure (cold stress or cold injury) on hepatic lipid metabolism. During the course of these studies, naturally, it has been important to study cold-acclimated animals as one of the control groups with which the acutely cold-stressed animals might be compared. For this reason some discussion of the hepatic lipid metabolism of the acutely cold-stressed rat is necessary in order to provide a proper framework for the findings in the cold-acclimated rat.

[1] This work was supported in part by Air Force Contract AF 41(657)321 monitored by the Alaskan Air Command, Arctic Aeromedical Laboratory; by Research Grant RG-4989 from the National Institutes of Health; and by a grant from the Whitehall Foundation.

LIVER LIPID AND GLYCOGEN LEVELS

In 1949 Sellers and You presented the first unequivocal evidence that cold-acclimation has a pronounced action on hepatic lipid metabolism. In these studies (1, 2) they found that the feeding of a hypolipotropic diet of moderate fat content causes an excessive hepatic fat deposit in rats living at room temperature but not in those living at 1.5°C. Sellers and You called this phenomenon the pseudolipotropic action of cold exposure. Treadwell *et al.* (3, 4) have obtained confirmatory evidence for this pseudolipotropic action of cold exposure. Perhaps even more striking is their finding (4) that the exposure of rats with nutritionally-induced fatty livers to a cold environment tends to restore the liver lipids to normal, although the animals continue to ingest a hypolipotropic diet.

Studies in our laboratory (5, 6) emphasize the complexity of the relationship between cold exposure and hepatic lipid levels. Before discussing these studies, however, we shall define certain abbreviations that will be used throughout this paper in order to eliminate repetitive descriptions of each set of experimental animals under discussion.

1) 'Control' refers to fed rats acclimated to 25°C.

2) 'Cold-fasted control' refers to rats acclimated to 25°C but fasted for 24 hours at 0°–2°C.

3) 'Cold-acclimated' refers to fed rats acclimated to 0°–2°C for 4 to 6 months.

4) 'Cold-fasted cold-acclimated' refers to rats acclimated to 0°–2°C for 4 to 6 months and fasted for 24 hours at 0°–2°C.

Other rat groups are used but infrequently; therefore these groups will be described when discussing the particular experiments.

The complexity of the relationship between cold exposure and hepatic lipid levels is particularly evident in the fasting response of the rat. When rats that are

TABLE 1. *Cold Acclimation and Hepatic Lipid and Glycogen Content; Cold Acclimation and Acetate and Palmitate Oxidation*

Physiological State	Liver Lipids	Liver Glycogen	% Acetate-1-C^{14} Conv. to $C^{14}O_2$*		% Palmitate-1-C^{14} Conv. to $C^{14}O_2$†	
			Without added glucose	With added glucose (0.02 M)	Without added glucose	With added glucose (0.02 M)
	% *wet wt.*					
Control	5.7±0.53 (5)	4.2±0.64 (5)	35±1.5 (5)	33±1.7 (5)	2.9±0.13 (4)	2.5±0.17 (4)
Cold-fasted control	11.8±0.64 (5)	0.3±0.12 (5)	12±0.8 (5)	32±2.5 (5)	2.6±0.20 (5)	4.3±0.40 (5)
Cold-acclimated	5.4±0.13 (6)	4.2±0.71 (6)	38±1.5 (6)	39±1.5 (6)	3.2±0.15 (5)	3.3±0.07 (5)
Cold-fasted cold-acclimated	5.7±0.35 (7)	2.0±0.17 (7)	37±1.2 (7)	42±1.2 (7)	3.7±0.17 (6)	4.7±0.16 (6)

Numbers in parentheses indicate number of rats used in each experiment. Values are means ± standard deviation of the mean. * The incubation flask contained 250 mg of tissue in 5 ml of Krebs-Henseleit bicarbonate buffer containing 5 μmoles of sodium acetate-1-C^{14}. The system was incubated for 3 hours at 37.5°C with continuous shaking. † Same incubation system as above except that 1.3 μmoles of palmitic acid-1-C^{14} was used instead of sodium acetate-1-C^{14}. Modified from Felts and Masoro (6).

acclimated to 25°C are either fasted at that temperature for 1 day or are fed at 0°–2°C for 1 day, a moderate elevation in hepatic lipid levels occurs. When the animals are fasted at 0°–2°C for 1 day ('cold-fasted control' rats) there is a pronounced rise in lipid levels. In a most striking manner, however, cold acclimation greatly alters the response of hepatic lipid level to fasting at 0°–2°C; in fact, no increase at all was found in the lipid content of the livers of 'cold-fasted cold-acclimated' rats. The data are summarized in table 1. It is clear, therefore, that the pseudolipotropic action of cold acclimation applies not only to hypolipotropic diets but to other factors causing fatty livers as well.

Moreover, cold acclimation alters the response to fasting not only in liver lipid but in liver glycogen levels as well. Liver glycogen is almost completely depleted when rats acclimated to 25°C are fasted for 24 hours at 0°–2°C, and it falls to less than 1 % wet weight when the rats are fasted 24 hours at 25°C. On the other hand, the liver glycogen level of the 'cold-fasted cold-acclimated' rats fell to only 2 % of wet weight (table 1). Of the several effects brought about by acclimation, this maintenance of liver glycogen is possibly the most dramatic. Pagé and Babineau (7) found that cold-acclimated rats fasting at room temperature also maintained higher liver glycogen levels than did fasted rats acclimated to room temperature. The relationship between hepatic lipid and glycogen levels is not entirely clear but some possibilities will be discussed below.

While the foregoing observations on liver lipid levels have yielded information that must be interpreted as meaning that cold acclimation profoundly affects hepatic lipid metabolism, the elucidation of the mechanisms involved awaits study at a molecular level. As a first approach to uncovering the underlying biochemical events, our laboratory embarked on an investigation of the effects of cold acclimation on fatty acid oxidation and fatty acid synthesis by *in vitro* liver systems.

HEPATIC ACETATE OXIDATION

In earlier work (8–10) we found that liver slices and homogenates from 'cold-fasted control' rats formed much less $C^{14}O_2$ from acetate-1-C^{14} and other short-chain fatty acids than did those prepared from 'control' rats. This defect in short-chain fatty acid oxidation could, it was found, be repaired by the addition of glucose to the incubation medium. Since the fasting, at a low environmental temperature, of rats acclimated to 25°C produced such marked changes in hepatic short-chain fatty acid oxidation, it was of interest to determine if cold acclimation would in any way modify the response. The results of such a study are summarized in table 1.

The most striking finding here is that cold acclimation abolishes the defect in hepatic acetate oxidation caused by fasting at low environmental temperatures. It is also noteworthy that the addition of unlabeled glucose to the incubation system had an appreciable effect only in the case of the liver slices from 'cold-fasted control' rats.

Although it is clear that cold acclimation greatly modifies the hepatic response to fasting at low environmental temperatures as far as acetate oxidation is concerned, the mechanism by which it prevents the depression in acetate oxidation is still somewhat obscure. The most likely explanation is that this maintenance of a high rate of hepatic acetate oxidation while fasting at 0°–2°C is secondary to the fact that the cold-acclimated rat is better able to sustain high levels of liver glycogen while fasting. The fact that the addition of large concentrations of glucose to the incubation medium vigorously promotes acetate oxidation only in the case of liver slices from 'cold-fasted control' rats lends support to this possibility.

HEPATIC PALMITATE OXIDATION

A somewhat more complicated picture emerged when the oxidation of long-chain fatty acids (palmitic, stearic and oleic) was studied (5). 'Cold-fasted control' rats were not defective in the hepatic oxidation of these acids. However, the addition of glucose to these liver slices from 'cold-fasted control' rats greatly enhanced the oxidation of the long-chain acids. Similar treatment of liver slices from 'control' rats resulted in the well-known sparing action that carbohydrate metabolism

exerts on fatty acid oxidation. It became of considerable interest, therefore, to study long-chain fatty acid oxidation by liver slices from fed and fasted cold-acclimated rats in both the presence and absence of unlabeled glucose. Palmitic acid-1-C^{14} was used as the substrate in the form of the albumin-palmitate complex, a most important transport form of fat (11); the results are summarized in table 1.

Two important findings emerge from this study. One is that liver tissue from 'cold-fasted cold-acclimated' rats in both the absence or presence of added glucose oxidizes significantly more palmitate than does liver tissue from 'control' rats. The other is that the addition of glucose to the medium promotes hepatic palmitate oxidation only in the case of the 'cold-fasted control' rats and the 'cold-fasted cold-acclimated' rats.

The finding of an increased rate of hepatic palmitate oxidation in the 'cold-fasted cold-acclimated' rat is a provocative one because it may well be causally related to the increased resistance to fatty infiltration of the liver and the increased fasting levels of glycogen previously noted for cold-acclimated rats. It is certainly not difficult to see that an increased rate of hepatic fatty acid oxidation should tend to prevent fatty infitration of the liver; likewise, an increased rate of fatty acid catabolism would be expected to spare glycogen utilization and thus tend to stabilize glycogen levels.

It is most interesting that the addition of glucose to the incubation medium promoted palmitate oxidation in both the glycogen-poor liver of the 'cold-fasted control' rat and the relatively glycogen-rich liver of the 'cold-fasted cold-acclimated' rat. This is excellent evidence that an almost complete absence of carbohydrate content is not a necessary condition for the demonstration of the fatty acid oxidation-promoting action of carbohydrate metabolism. However, fasting in the cold appears to be one of the very few physiologic conditions in which the classic aphorism "fat burns in the flame of carbohydrate" can be experimentally demonstrated. In most other circumstances the sparing action of carbohydrate metabolism on fat catabolism appears to dominate (12).

HEPATIC FATTY ACID SYNTHESIS

We shall now turn from fatty acid oxidation to the reverse process, namely the process of fatty acid synthesis. However, it should be kept in mind that the intermediary metabolic pathway of fatty acid synthesis is not merely a reversed pathway of fatty acid oxidation (13, 14).

The ability of liver slices to convert acetate-1-C^{14} to fatty acid-C^{14} was measured for both the 'control' and the 'cold-acclimated' rats (15). Table 2 contains a brief summary of the findings.

It is evident that liver slices from 'cold-acclimated' rats have a greatly reduced ability to convert acetate-1-C^{14} to fatty acids. Since the glycogen content of the liver from 'cold-acclimated' rats is the same as that of the 'control' rats the inhibition of hepatic lipogenesis

TABLE 2. *Cold Acclimation and Hepatic Fatty Acid Synthesis*

Physiological State	No. of Rats	Glycogen Content % *wet wt.*	% Acetate-1-C^{14} Recovered in Fatty Acids*
Control	14	4.2±0.35	5.9±1.26
Cold-acclimated	15	4.1±0.31	1.8±0.31

Values are means ± standard deviation of the mean. *Incubation system and procedure same as that described for acetate oxidation in table 1. Modified from Masoro *et al.* (15).

TABLE 3. *Disappearance of Liver Glycogen from Liver Slices During Incubation*

Physiological State	No. of Rats	% Change in Glycogen Content During Incubation*
Control	2	−76
Cold-acclimated	4	−82

* Incubation procedure same as that described for acetate oxidation in table 1. Modified from Masoro *et al.* (15).

cannot be related in any simple way to a lack of carbohydrate substrate, an explanation that certainly seems to hold in the case of the depressed hepatic lipogenesis of the cold-stressed rat (16).

It is certainly possible that the liver slices from the 'cold-acclimated' rat are not able to utilize their endogenous glycogen during the course of the incubation. If such were the case, it is to be expected that the net disappearance of glycogen during incubation should be quite low in the case of liver slices from 'cold-acclimated' rats. However, from the results summarized in table 3, it is clear that the net disappearance of glycogen from the liver slices during the incubation is similar in the two groups of animals, thus making it unlikely that the reduction in hepatic lipogenesis in the 'cold-acclimated' rat results from an inability to mobilize liver glycogen.

Of course, it is possible that other abnormalities in carbohydrate metabolism might be present. For instance, the utilization of glucose via hexokinase might be blocked in the livers of the 'cold-acclimated' rats, thus making glucose produced by glycogenolysis unavailable for further metabolic activity; or the pathways of glucose catabolism may be altered so that the hexose-monophosphate pathway is not operating at an appreciable rate in the liver of the 'cold-acclimated' rat. The first of these possibilities was investigated by measuring the production of $C^{14}O_2$ from labeled glucose (0.02M) by the liver slices. The second hypothesis was tested by

TABLE 4. *Cold Acclimation and Hepatic Glucose Oxidation*

Physiological State	% Glucose-1-C^{14} Conv. to $C^{14}O_2$	% Glucose-6-C^{14} Conv. to $C^{14}O_2$	Ratio of $C^{14}O_2$ from glucose-6-C^{14}: $C^{14}O_2$ from glucose-1-C^{14}*
Control	2.77±0.224	1.72±0.060	0.62±0.057
Cold-acclimated	2.39±0.255	1.82±0.146	0.71±0.033

Seven rats used in each experiment. Values are means ± standard deviation. *Incubation is the same as that described for acetate oxidation in table 1 except that 100 μmoles of labeled glucose was used instead of sodium acetate-1-C^{14}. Modified from Masoro *et al.* (15).

XUM

measuring the ratio of $C^{14}O_2$ produced by the slices from glucose labeled in position 1 and from glucose labeled in position 6, respectively (17). The results of the study are summarized in table 4.

It is clear that liver slices from the 'control' rats and those from the 'cold-acclimated' rats oxidize about the same amount of labeled glucose. Furthermore, the ratio of $C^{14}O_2$ formed from glucose-6-C^{14} to that formed from glucose-1-C^{14} is not significantly changed by cold acclimation. The latter data suggest then that the hexose-monophosphate pathway of carbohydrate metabolism is functioning normally in the livers of 'cold-acclimated' rats. A note of caution must be interjected, however, because factors other than the hexose-monophosphate pathway of metabolism are known to influence relative yields of $C^{14}O_2$ from glucose-1-C^{14} and glucose-6-C^{14} (18). Along this line of thought Dr. Hannon presented evidence earlier today on the glucose-6-phosphate dehydrogenase levels of the livers of cold-acclimated rats which would seem to contradict our conclusions from the glucose-1-C^{14} and glucose-6-C^{14} studies. However, the interpretation of enzyme level data must also be done with caution, because it is difficult to establish that the enzyme level is the limiting factor in an *in vivo* metabolic process. With these reservations in mind we may conclude that the depressed hepatic lipogenesis of the 'cold-acclimated' rat does not result from an inability of the liver to oxidize adequate amounts of carbohydrate nor from an alteration in pathways of carbohydrate oxidation.

In recent years much work has led to the conclusion that carbohydrate metabolism plays the prime role in the regulation of the rate of lipogenesis (19). The general interpretation is that a phase of carbohydrate metabolism in either the Embden-Meyerhof or the hexose-monophosphate pathway of carbohydrate metabolism promotes the rate of acetyl coupling into fatty acids. Quite recently strong evidence (20) has indicated that the generation of reduced triphosphopyridine nucleotide (TPNH) in the hexose-monophosphate pathway of carbohydrate metabolism is the biochemical mechanism by which carbohydrate metabolism stimulates lipogenesis.

However, the work of Spirtes *et al.* (21) shows that other important regulators must be involved in setting the rate of fatty acid synthesis. These workers found a high rate of lipogenesis in liver slices of hyperthyroid rats, although the glycogen content of the liver was extremely low. Obviously, in the case of these slices little carbohydrate metabolism could have been occurring. Therefore, in the hyperthyroid rat, metabolic factors other than carbohydrate metabolism must promote lipogenesis.

On the other hand, in the case of the 'cold-acclimated' rat we have evidence of metabolic alterations capable of limiting hepatic lipogenesis in the face of a high rate of carbohydrate metabolism. Obviously, therefore, the regulation of lipogenesis is more complicated than the explanation that relates lipogenesis only to carbohydrate utilization. It would seem that an understanding of the metabolic factors which limit hepatic lipogenesis in the 'cold-acclimated' rat would do much to further elucidate the regulatory apparatus controlling the rate of lipogenesis.

For this reason our laboratory embarked on a detailed study at a molecular level of hepatic lipogenesis in the 'cold-acclimated' rat. Cell-free liver homogenates were used in this study. The composition of the incubation medium is given below:

0.12 M KCl
1.5×10^{-2} M $MnCl_2$
2.5×10^{-3} M Sodium acetate-1-C^{14}
2.5×10^{-3} M Potassium succinate
4.7×10^{-2} M Isocitrate, trisodium
4×10^{-3} M Triphosphopyridine nucleotide (TPN)
1.2×10^{-3} M Potassium phosphate (pH of medium = 7.0)
3×10^{-3} M Diphosphopyridine nucleotide (DPN)
2.9×10^{-4} M Coenzyme A (CoA)
2×10^{-2} M $KHCO_3$

It is important to point out that triphosphopyridine nucleotide (TPN) and isocitrate were used at experimentally determined optimal levels and that the absence of either TPN or isocitrate in this system abolished lipogenesis. It was also established that the rate of TPNH generation is not the rate-limiting factor in the lipogenic activity of this system. Under these specific conditions we found that liver homogenates from 'control' and 'cold-acclimated' rats formed fatty acids from acetate at similar rates. It is evident, therefore, that when an optimal cofactor environment is provided, there is no defect in the hepatic lipogenic capacity of the 'cold-acclimated' rat. One must further conclude that the enzymes involved in lipogenesis are present in adequate amounts in the livers of 'cold-acclimated' rats. Why then the low rate of lipogenesis in the intact liver cell of the 'cold-acclimated' rat? Two possibilities are now being investigated. One is that in the intact liver cell TPNH generation does not adequately supply the fatty acid synthesizing system in the case of the 'cold-acclimated' rat. This could result from a low hexose-monophosphate pathway activity, as indicated by Dr. Hannon's work, or it could be due to a failure in the coupling of the TPNH generation of a normal hexose-monophosphate pathway activity with the fatty acid synthesis process. The latter would be more in line with our findings that there is an apparently normal hexose-monophosphate pathway activity in the intact liver cell of the 'cold-acclimated' rat. The second possibility is that in the process of fortifying the homogenate system, a cofactor that is in short supply in the intact liver cell of the 'cold-acclimated' rat is now being supplied in adequate quantities for a normal rate of lipogenesis to occur.

It is thus seen that cold acclimation provides us with an excellent tool for the study of the physiologic regulation of hepatic lipogenesis and for this reason alone the study of lipogenesis in these animals should be vigorously

pursued. However, a further question might be asked: What, if any, role does this reduction in hepatic lipogenesis play in the ability of the animal to successfully cope with an unfavorably cold environment? Although the alterations in the small mammal which we call cold acclimation are undoubtedly the result of changes at the level of intermediary metabolism, it is difficult to relate the reduction in hepatic lipogenesis to survival in a cold environment. However, it seems likely that metabolic regulators such as cofactor levels are shifted in the cold-acclimated animal in such a way as to promote maximum oxidative metabolic activity. If such be the case, the reduction in hepatic lipogenesis may occur merely as an inevitable by-product of the changes in intermediary metabolism essential for existence at low environmental temperatures.

GENERAL CONCLUSIONS

Two rather distinct kinds of information have been made available by experimentation on hepatic lipid metabolism in the cold-acclimated rat. First, further insight has been gained concerning the acclimation process as it occurs at the molecular level of organization. Second, the cold-acclimated animal has provided and continues to provide a powerful tool for the study of the physiologic regulators of intermediary metabolism.

In regard to the first point, the main aim of our work has been to find a mechanistic explanation for the following two phenomena: *1*) the great capacity of the cold-acclimated rat to resist fatty infiltration of the liver; *2*) the ability of the cold-acclimated rat to maintain liver glycogen at surprisingly high levels during fasting.

A rational explanation for both phenomena is provided by the findings presented here, namely that the liver of fasted cold-acclimated rats has an increased capacity to oxidize long-chain fatty acids. If the liver is capable of burning more of the fat transported to it, one can readily imagine that there is a decreased likelihood of fat deposition in the liver. It is also apparent that if the liver is capable of burning more of the fat transported to it during fasting, less glycogen will be oxidized, thus providing a more stable maintenance of liver glycogen during fasting.

Turning now to the use of the cold-acclimated rat as a tool for the study of the physiologic regulation of intermediary metabolism, one sees that this work has led to two important findings.

First, studies on the liver of both cold-acclimated and cold-stressed rats have yielded the first unequivocal evidence in support of the classical aphorism—"fat burns in the flame of carbohydrate." Moreover, our work has led to at least a partial understanding of the mechanism by which carbohydrate metabolism promotes fatty acid oxidation (10). Further work along this line should prove quite fruitful.

Second, the study of the cold-acclimated rat has provided new evidence concerning the regulation of hepatic lipogenesis. The failure of hepatic lipogenesis in the cold-acclimated rat has been shown to be unrelated to an abnormal carbohydrate metabolism. Therefore, powerful regulators of lipogenesis in the liver must exist aside from the well-known regulating action of carbohydrate metabolism.

It is our hope that further work on the cold-acclimated rat may provide an opportunity to discover the nature of these regulators.

REFERENCES

1. Sellers, E. A. and R. W. You. *Science* 110: 713, 1949.
2. Sellers, E. A. and R. W. You. *Biochem. J.* 51: 573, 1952.
3. Treadwell, C. R., D. F. Flick and G. V. Vahouny. *J. Nutrition* 63: 611, 1957.
4. Treadwell, C. R., D. F. Flick and G. V. Vahouny. *Proc. Soc. Exper. Biol. & Med.* 97: 434, 1958.
5. Masoro, E. J. and J. M. Felts. *J. Biol. Chem.* 231: 347, 1958.
6. Felts, J. M. and E. J. Masoro. *Am. J. Physiol.* 197: 34, 1959.
7. Pagé, E. and L. M. Babineau. *Canad. J. Biochem. & Physiol.* 32: 395, 1954.
8. Masoro, E. J., A. I. Cohen and S. S. Panagos. *Am. J. Physiol.* 180: 341, 1955.
9. Masoro, E. J., S. S. Panagos, A. I. Cohen and D. Rapport. *Am. J. Physiol.* 186: 24, 1956.
10. Masoro, E. J. and J. M. Felts. *J. Biol. Chem.* 234: 198, 1959.
11. Fredrickson, D. S. and R. S. Gordon, Jr. *Physiol. Rev.* 38: 585, 1958.
12. Lossow, W. J. and I. L. Chaikoff. *Arch. Biochem. and Biophys.* 57: 23, 1955.
13. Brady, R. O. *Proc. Natl. Acad. Sci. U.S.* 44: 993, 1958.
14. Wakil, S. J., E. B. Titchener and D. M. Gibson. *Biochim. et biophys. acta* 34: 227, 1959.
15. Masoro, E. J., J. M. Felts and S. S. Panagos. *Am. J. Physiol.* 189: 479, 1957.
16. Masoro, E. J., A. I. Cohen and S. S. Panagos. *Am. J. Physiol.* 179: 451, 1954.
17. Bloom, B. and D. Stetten. *J. Am. Chem. Soc.* 75: 5446, 1953.
18. Wood, H. G. *Physiol. Rev.* 35: 841, 1955.
19. Chaikoff, I. L. *Harvey Lectures* (1951–52) p. 99.
20. Siperstein, M. D. *Am. J. Med.* 24: 685, 1959.
21. Spirtes, M. A., G. Medes and S. Weinhouse. *J. Biol. Chem.* 204: 705, 1953.

Metabolism of serum-free fatty acids

R. S. GORDON, JR.
Section on Metabolism, Laboratory of Cellular Physiology and Metabolism, National Heart Institute, Bethesda, Maryland

GORDON, R. S., JR. *Metabolism of serum-free fatty acids.* Fed. Proc. 19, Suppl. 5: 120–121. 1960.—Circulating free fatty acids are derived from peripheral adipose tissue and travel in the blood plasma as a complex with albumin. Among the numerous hormones that affect the release of fatty acids, norepinephrine and epinephrine are the most effective in increasing the rate of release from adipose tissue. The increased production of these hormones under the stress of cold could result in a greater than normal mobilization of free fatty acids necessary for energy production.

I HAVE BEEN ASKED TO SUMMARIZE for this conference recent advances in research on the physiological significance of the free fatty acids of plasma (FFA, also called nonesterified or unesterified fatty acids), not because any direct relationship between FFA and cold adaptation has yet been demonstrated, but because there may be opportunities for future research in this field. A recent review (1) should be consulted for a more complete survey of the subject, and for more references than it is possible to give at this time.

Free fatty acids, like free cholesterol, do not exist in true solution in blood plasma, but are bound by serum proteins. In the case of the fatty acid anions (for they are fully dissociated at the pH of plasma), the carrier protein is primarily albumin. The interaction of albumin with fatty acid anions has recently been studied in detail (2). In spite of the strong interaction between these fatty acids and the albumin, however, the fatty acids are able to leave the vascular compartment at very rapid rates, far exceeding the turnover rate of the carrier protein (3).

That free fatty acids are utilized as substrates for cellular oxidation and energy production seems now to be well established. Evidence derived from the measurement of arteriovenous differences in free fatty acid concentration (4) indicates that large quantities of fat in this form are delivered to the myocardium and to the abdominal viscera during fasting, but that the administration of glucose and insulin causes an abrupt termination of this transport process. That the fate of the fatty acid is oxidative catabolism has been demonstrated by tracer studies with C^{14}-labeled fatty acids both in animals (5, 6) and in man (7). Utilization of labeled free fatty acid presented as the albumin complex has also been shown in tumor cells incubated *in vitro* (8).

As surmised by Favarger as long ago as 1946 (9), it has been shown that the source of the circulating free fatty acids is peripheral adipose tissue. Measurement of arteriovenous differences (4) demonstrates this fact for human subjects, and the liberation of free fatty acids from surviving adipose tissue incubated *in vitro* has been reported subsequently (10).

Many chemical, hormonal and probably even neural influences act on the adipose tissue to govern its rate of release of free fatty acids. These phenomena were first observed as effects of various nutritional and hormonal stimuli on the concentration of circulating free fatty acid, but many aspects have since been studied more carefully in the isolated adipose tissue system. Just to list the agents that affect the circulating FFA concentration in intact animals, or influence the rate of output of FFA from isolated adipose tissue, will require a considerable fraction of the time at our disposal.

Among the more important nutritional effects are the reduction in FFA levels produced by glucose and insulin (11), the effect of these same agents in inhibiting output of FFA from adipose tissue (10), the decrease in FFA levels resulting from the oral administration of amino acids to man (4), and the marked increase that occurs when artificial fat emulsions are administered intravenously (12). Hormonal influences that have been established include that of insulin, mentioned above; the effect of growth hormone, which elevates FFA levels *in vivo* (13); the effect of ACTH on the release of FFA from adipose tissue *in vitro* (14); the action of thyroid hormone in increasing the FFA level in man (15); the effects of glucagon, which appears to act in two ways, first, by mobilizing glucose, which causes a decrease in FFA levels (16), and later, by some other means, to increase FFA levels (M. B. Lipsett *et al.* (16a)); the dramatic increases in FFA levels produced by epinephrine (11, 17), which have since been shown with isolated adipose tissue (10, 18), and which appear to require the function of the adrenal cortex for their manifestation (19); and the very similar effects of norepinephrine (20). The possibility of a direct effect of the nervous system on the mobilization of FFA is suggested by studies showing an increase in FFA concentrations in response to anxiety (21, 22) and by the finding that pharmacologic agents which inactivate the sympathetic nervous system produce a fall in FFA levels (20).

Two potentially productive lines of research suggest themselves when one views these findings in the context

of this symposium on cold acclimation. The first would be studies directed at investigating the possibility that alterations in endocrine function, occurring in response to exposure to cold, may affect the mobilization of depot fat as FFA, and thus alter the availability of fatty acids for energy production. The second would be concerned with the effects of lowered environmental temperature on the physiology of adipose tissue, since this tissue, in its superficial location, would naturally be subject to temperature variations imposed from without. No data available at present bear at all on this latter subject. Perhaps at future meetings there will be papers concerned with the role in cold adaptation of alterations in FFA metabolism.

REFERENCES

1. FREDRICKSON, D. S. AND R. S. GORDON, JR. *Physiol. Rev.* 38: 585, 1958.
2. GOODMAN, D. S. *J. Am. Chem. Soc.* 80: 3892, 1958.
3. HAVEL, R. J. AND D. S. FREDRICKSON. *J. Clin. Invest.* 35: 1025, 1956.
4. GORDON, R. S., JR. *J. Clin. Invest.* 36: 810, 1957.
5. MCCALLA, C., H. S. GATES, JR. AND R. S. GORDON, JR. *Arch. Biochem. Biophys.* 71: 346, 1957.
6. FREDRICKSON, D. S., D. L. MCCOLLESTER AND K. ONO. *J. Clin. Invest.* 37: 1333, 1958.
7. FREDRICKSON, D. S. AND R. S. GORDON, JR. *J. Clin. Invest.* 37: 1504, 1958.
8. FILLERUP, D. L., J. C. MIGLIORE AND J. F. MEAD. *J. Biol. Chem.* 233: 98, 1958.
9. FAVARGER, P. *Schweiz. Med. Wchnschr.* 76: 1342, 1946.
10. GORDON, R. S., JR. AND A. CHERKES. *Proc. Soc. Exper. Biol. & Med.* 97: 150, 1958.
11. DOLE, V. P. *J. Clin. Invest.* 35: 150, 1956.
12. MOELLER, H. C., M. I. GROSSMAN, L. PALM, A. CUSHING, J. B. STADLER AND G. H. BECKER. *J. Lab. & Clin. Med.* 46: 450, 1955.
13. RABEN, M. S. AND C. H. HOLLENBERG. *J. Clin. Invest.* 38: 484, 1959.
14. WHITE, J. E. AND F. L. ENGEL. *J. Clin. Invest.* 37: 1556, 1958.
15. RICH, C., E. L. BIERMAN AND I. L. SCHWARTZ. *J. Clin. Invest.* 38: 275, 1959.
16. BIERMAN, E. L., V. P. DOLE AND T. N. ROBERTS. *Diabetes* 6: 475, 1957.
16a. LIPPSETT, M. B., H. R. ENGEL AND D. M. BERGENSTAL. *J. Lab. & Clin. Med.* 56: 342, 1960.
17. GORDON, R. S., JR. AND A. CHERKES. *J. Clin. Invest.* 35: 206, 1956.
18. WHITE, J. E. AND F. L. ENGEL. *Proc. Soc. Exper. Biol. & Med.* 99: 375, 1958.
19. SHAFRIR, E. AND D. STEINBERG. *J. Clin. Invest.* 39: 310, 1960.
20. HAVEL, R. J. AND A. GOLDFIEN. *J. Lipid Research* 1: 102, 1959.
21. BOGDONOFF, M. D., E. H. ESTES, JR. AND D. TROUT. *Proc. Soc. Exper. Biol. & Med.* 100: 503, 1959.
22. CARDON, P. V, JR. AND R. S. GORDON, JR. *J. Psychosomat. Research* 4: 5, 1959.

Comments on intermediary metabolism in relation to cold

R. B. MEFFERD, JR.

Psychiatric and Psychosomatic Research Laboratory, Houston Veterans Administration Hospital and Baylor University College of Medicine, Houston, Texas

MEFFERD, R. B., JR. *Comments on intermediary metabolism in relation to cold.* Fed. Proc. 19, Suppl. 5: 121–124. 1960.—Changes in lipid and protein metabolism during adaptation to cold indicate shifts in metabolic interrelationships which contribute to homeostasis. In the past, the univariant approach has been used to acquire the needed basic information concerning changes in metabolism during acclimation to cold. It is time the multivariant approach was used to correlate the individual qualitative as well as quantitative changes that contribute to the metabolic steady state. In the general pattern of response, small variations in one area of metabolism may be as significant as large variations in another. A specific example of the univariant factor in a multivariant situation is that of the increased creatine excretion in the cold by animals that are not shivering. Data from urine specimens are presented to show the interrelationship of the products of metabolism under differing environmental conditions.

I WOULD LIKE TO OPEN MY DISCUSSION with a few remarks on both Dr. Trapani's and Dr. Masoro's papers. The demonstration by Dr. Masoro that the rates of oxidation and of synthesis of fatty acids by the liver differ in the cold-acclimated and control rats is important. His experimental approach represents a necessary appreciation of the basic differences between the anabolism and catabolism of these acids. He and I have compared our separate results on lipid metabolism (1) and agree that there probably is no conflict in them. As he has pointed out, the liver actually has a relatively small total role in lipid metabolism. Accordingly, it is not surprising that we found that, along with many other physiological rates, total body lipid anabolic rates of cold-acclimated rats also were elevated. Apparently, however, at certain

sites, such as the liver, there are important shifts in some of the mechanisms involved. This should be a rewarding area for further study.

I was greatly impressed by the ingenuity shown in Dr. Trapani's approach to the problem of protein metabolism in cold-acclimated rabbits. This area of metabolism holds considerable promise, I feel. Our own work has shown that in cold-acclimated rats as compared to controls the excretion rates of the various amino acids differ markedly, and that many of these differential effects are relatively independent either of food intake or of amount of body weight loss during a short fast. Like Dr. Trapani we have obtained considerable evidence in rats that there are cold-induced changes in protein metabolism, especially with gastrocnemius and diaphragm myoglobin and with liver and adrenal succinic dehydrogenase, although we found no differences in the total erythrocytes, hematocrit or hemoglobin (2). I would suggest that in addition to electrophoretic analysis of blood proteins the specificities (i.e. differences) of the antibodies formed during active immunization in the different environments might profitably be compared by sensitive immunological means, e.g. with the Ouchterlony agar diffusion technique. Dr. Trapani's use of the rate of homologous antibody decay in passively immunized rabbits as his experimental criterion of protein turnover is advantageous in several respects. I personally feel, however, that active immunization processes also might be so manipulated as to provide additional useful information. For example, the anamnestic immunological response might be utilized to provide a measure of immune responsitivity per se in cold-acclimated rabbits, where the passive transfer technique provides suggestive evidence only. Another complication lies in the exquisite specificity of even homologous proteins, i.e. some or all of the passively transferred homologous antibody molecules actually might be sufficiently foreign so that they act as antigens themselves, thus complicating the decay process. This perhaps minor problem will exist in all strains except those that are very highly inbred, that is, where the serum is isologous. The extent of this problem could be appraised also by means of one of the gel-diffusion techniques. Another more difficult approach that might provide substantiating evidence of the differences in protein turnover rates would be to utilize the rates of adaptive enzyme formation and decay. All in all, protein metabolism in the cold is a fertile field.

It is my feeling that, with processes as complex as these with which we are dealing here, we have almost arrived at the point of diminishing returns with the univariant experimental approach. It appears that most of the changes that have been observed to occur in the cold are purely quantitative ones. As occurs when we depress the throttle of a motor, everything speeds up, but the processes retain their relative relationship to one another. If we limit our investigations to these phenomena, we will learn virtually nothing about the mechanisms involved. The quantitative changes may be explained, for example, by such compensatory factors as increased food consumption. To gain further understanding we must delve into possible differential changes, i.e. changes in the interrelationship of the variables and processes, or qualitative changes. This a priori requires a multivariate approach. But more than this, for the greatest information yield, the variables measured should be evaluated simultaneously rather than one at a time, i.e. by a multivariate technique of analysis such as factor analysis. Unless the latter is done, regardless of the number of variables actually measured, we have used in essence a univariate approach applied, it is true, to several variables; but this is not a multivariate approach. Slight differences in a given variable may not in themselves be statistically significant, yet when these are combined with concomitant changes, among other interrelated variables, very real differences may emerge.

Collation of information from different investigations on possible qualitative changes specific to cold acclimation is difficult at best, since we all, being rugged individualists, insist upon using widely varying experimental procedures, e.g. air temperature, movement and humidity, length of exposure, lighting schedule, kind of diet, and age, strain and sex of animals, etc. Of especial importance in this respect is the treatment that the animals, or man as far as that goes, have received preceding the experiment. Heat- or altitude-acclimated rats, for example, respond quite differently in many respects to cold exposure than do neutral acclimated ones (3). Procedural variations such as these would be expected to exert an especially strong influence in experiments where primarily compensatory or quantitative changes are involved, as is the case in cold acclimation. Caution is advisable, therefore, when we attempt to generalize about qualitative changes specific to cold.

Notwithstanding this, however, certain pertinent relationships are beginning to emerge. One of these relates to the fact now observed by several investigators that, after an initial rather sharp increase, the food intake of cold-exposed rats increases thereafter at a slower but steady rate for many weeks during which time body weight remains practically constant. Why do the rats steadily increase their intake even after they apparently are acclimated? This approximate doubling of food intake after 10–12 weeks results in high nutrient turnover and inefficient utilization—so much so in fact that variables, ordinarily significantly correlated with food intake in other environments, no longer are so in the cold (4).

To illustrate other pertinent items and possible qualitative changes, I would like to present very briefly part of an unpublished experiment involving fasting of 8-months acclimated rats carried out by Dr. H. B. Hale and myself while I was at the Clayton Foundation Biochemical Institute of the University of Texas. Ten rats each (Sprague-Dawley males of similar ages) were selected at random from groups acclimated to cold (2.5°C), neutral temperature (25°C), or heat (35°C). These rats then lived in their respective acclimated

TABLE 1. *Influence of the Acclimated State (Past History) of Rats on Urinary and Other Variables During Fasting*

Environmental Group*	Means (per Rat) on Consecutive Days				Statistical Details‡					
	1st-3rd Nonfast†	4th Fast	5th Fast	6th Fast	C.D. between Groups	C.D. between Days	$\sqrt{MS_w}$	Pertinent significant 'F' ratios *bg*	*bd*	*g*×*d*
				Water intake (ml/day)						
Cold	45.0	8.7	6.8	2.4	9.5	3.4	12.1	9.1	2.93	n.s.
Neutral	33.9	21.8	18.2	23.1						
Hot	47.5	39.3	39.5	39.5						
				Urine volume (ml/day)						
Cold	20.6	11.3	8.2	5.1	4.5	2.9	6.54	3.92	10.	8.66
Neutral	8.7	9.4	4.4	6.7						
Hot	9.7	14.0	13.4	13.3						
				Urinary specific gravity						
Cold	1.046	1.035	1.031	1.042	.011	.008	.0151	9.0	4.31	2.97
Neutral	1.044	1.044	1.023	1.028						
Hot	1.032	1.019	1.016	1.011						
				Creatine (mg/day)						
Cold	6.4	7.6	9.2	12.8	1.9	1.6	.625	334.	206.	39.
Neutral	1.3	1.5	1.8	1.8						
Hot	1.2	1.3	2.5	2.8						
				Creatinine (mg/day)						
Cold	8.6	8.3	9.6	9.1	1.7	1.0	1.45	15.	4.15	5.64
Neutral	7.9	7.0	6.9	7.3						
Hot	13.0	13.4	8.3	9.7						
				pH						
Cold	6.7	6.2	6.4	6.2	.16	.11	.261	23.	62.	7.44
Neutral	7.3	6.5	6.2	6.5						
Hot	7.3	7.1	6.7	6.7						
				Total titratable acid (mEq/day)						
Cold	5.89	14.2	12.8	11.6	1.36	.89	2.12	44.	50.	8.52
Neutral	5.61	11.1	10.1	7.78						
Hot	3.69	4.81	5.75	5.66						
				Phosphate (as P) (mEq/day)						
Cold	1.65	2.27	2.01	2.08	.27	.12	.371	33.	20.	8.33
Neutral	1.36	1.76	1.21	.85						
Hot	.62	1.02	.95	.82						
				Ketones (mg/day)						
Cold	10.1	8.41	11.0	9.69	1.5	1.2	2.56	9.7	18.	4.63
Neutral	14.1	10.6	12.1	13.1						
Hot	12.2	4.41	7.95	7.02						
				Feces dry weight (gm/day)						
Cold	6.92	.90	.44	.65	.45	.34	.530	39.	146.	149.
Neutral	5.26	.71	.94	.38						
Hot	3.33	1.12	.15	.14						

* Ten rats per group. † Averaged. ‡ Explanation of terms: *C.D.* = critical difference ($p = .05$); a '*t*' test of the difference between any pair of means may be performed simply by comparing it with the suitable C.D., *i.e.* between environmental groups on any given day from the first C.D. given, and between days from the second. $\sqrt{MS_w}$ = estimate of average standard deviation. '*F*' ratios = *bg* (between environmental groups), 2 degrees of freedom; *bd* (between days), 5 degrees of freedom; and $g \times d$ (groups × days interaction), 10 degrees of freedom. If the latter *F* is significant, the groups changed differently from one another during the fast.

environments in plastic-coated metabolism cages for 7 days (to become accustomed to the cages) preceding a 6-day experimental period (3 days nonfast and 3 days fast). Purina Lab Chow and water were supplied ad libitum and clean cages were provided daily. The 24-hour urine samples were collected into sufficient thymol to inhibit microbial growth and two drops of octyl alcohol were added to the collection vessels to inhibit evaporation. At the start, mean body weight and food intake for the cold, neutral and heat groups respectively (standard deviations in parentheses) were: 393 (59) gm and 32.7 (5.9) gm/day; 441 (57) gm and 20.1 (3.6) gm/day; and 333 (39) gm and 13.2 (1.9) gm/day. The percentage weight losses in each group were almost

identical on succeeding days of fast and averaged 10.8, 10.5 and 10.4 for the respective groups. Although the heat-acclimated rats weighed less than their very lean cold counterparts, they had extensive fat deposits, while the neutral rats were moderately lean. Table 1 presents the results of several variables that are pertinent to this discussion. I call attention to the sharp drop in water intake during the fast in the cold group, to the continued relatively high urine volume, and to the maintenance of a high urinary specific gravity. This striking drop in water intake has been noted in other investigations and appears to be characteristic.

The shift from shivering to nonshivering thermogenesis (5) that is completed after about a month's exposure might be expected to involve changes in creatine and creatinine excretion. Unfortunately, no time-course data are available on the former, but the latter increased by 25% during the first 2 weeks and maintained this until the 10th week when it returned to normal (6). This return to pretest levels corresponded to the final plateauing in food intake. In the fasting experiment (table 1) urinary creatinine was slightly elevated in the cold group after 8 months, but creatine was very greatly elevated in the nonfasting rats, and it increased further during fasting. These rats were not shivering. What is the source of and the mechanism involved in the large quantities of creatine excreted? Are the muscles involved?

My final point relates to fasting ketonuria in cold-acclimated rats. The urinary pH of these rats was low while the total titratable acid (titrated to pH 7.4) was high throughout the experiment. There was no ketonuria (7), however, in these lean long-term cold-acclimated rats.

I will close by using the data in table 1 to illustrate how difficult it is to arrive at a steady state in this work (*e.g.* the differences in amount of food in, and the emptying time of, the intestinal tract at any given time) and as a consequence of the difficulties inherent in attempting to compare environmental groups in a meaningful manner. Perhaps this is especially true in lipid studies since fasting, ambient temperature, diet, stores or pools of neutral body fat, and many other factors so strongly influence the results.

Attendance at this meeting was made possible by financial assistance from the Clayton Foundation Biochemical Institute and the Hogg Foundation for Mental Health of the University of Texas; from the Department of Physiology, Baylor University College of Medicine; and from the Federation of American Societies for Experimental Biology.

REFERENCES

1. Mefferd, R. B., Jr., M. A. Nyman and W. W. Webster. *Am. J. Physiol.* 195: 744, 1958.
2. Criscuolo, D., H. B. Hale and R. B. Mefferd, Jr. *J. Appl. Physiol.* 13: 353, 1958.
3. Mefferd, R. B., Jr. and H. B. Hale. *Am. J. Physiol.* 195: 726, 1958.
4. Mefferd, R. B., Jr. and H. B. Hale. *Am. J. Physiol.* 193: 443, 1958.
5. Hart, J. S. *Fed. Proc.* 17: 1045, 1958.
6. Hale, H. B. and R. B. Mefferd, Jr. *Am. J. Physiol.* 194: 469, 1958.
7. Greenburg, L. A. and D. Lester. *J. Biol. Chem.* 154: 177, 1944.

Effects of exposure to cold on coenzyme A levels in liver tissue[1]

J. CAMPBELL, G. R. GREEN, E. SCHÖNBAUM[2] AND H. SOCOL
Department of Physiology and the Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada

Campbell, J., G. R. Green, E. Schönbaum and H. Socol. *Effects of exposure to cold on coenzyme A levels in liver tissue.* Fed. Proc. 19, Suppl. 5: 124–125. 1960.—In rats exposed to cold for 24 days, a 60% increase occurs in the concentration and amount of coenzyme A in the liver. Also under these conditions the oxidation of fatty acids is accelerated, while the acetylating capacity of the rat is decreased.

Changes in metabolic state often induce alterations in enzymatic activities in tissues (1). An exploration of the biochemistry of adaptation to cold and of the mechanisms facilitating the increase of metabolic rate observed

[1] This investigation was aided by grants from the Defence Research Board of Canada (Grant No. 8865-04) and the University of Toronto Advisory Committee on Scientific Research.

[2] Present address: Department of Pharmacology, University of Toronto.

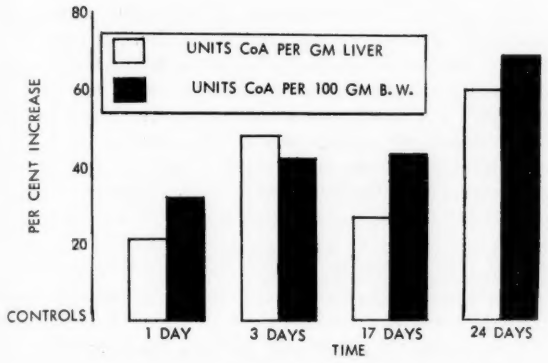


FIG. 1. Effect of exposure of rats to the environmental temperature of 0° to 2°C on the coenzyme A level in the liver. The percentage increase in hepatic coenzyme A over that in the control rats at room temperature is shown.

during exposure to cold was therefore started with an investigation of the effects of exposure to cold and of diet on coenzyme *A* (CoA) levels in the tissues of the rat. The results of this investigation (2) are summarized herein.

METHODS

Male rats of the Wistar strain were kept in individual cages at the usual environmental temperature of 23°C, or in the cold at 0–2°C in rooms with circulation of air. The purified isocaloric diets, provided ad libitum, all contained 21% protein, 12% fat and 60.5% carbohydrate. The rats were killed by decapitation and samples of tissue were dissected, weighed and frozen within 3 minutes. CoA was extracted and determined by the methods of Kaplan and Lipmann (3), or of Tabor *et al.* (4).

RESULTS AND DISCUSSION

The rats kept in the cold either lost weight or gained relatively slowly, and their reserves of depot fat were low despite increased intakes of food. The adrenals, heart and kidneys were enlarged in proportion to body weight, but the liver weight did not change. The extractable CoA content of the liver increased early in the period of adaptation to cold and remained high during continued exposure (fig. 1). These increases were significant whether liver CoA was calculated on the basis of fresh tissue, or of the solids of the tissue, or of whole-body weight.

It is easy to suggest a teleological explanation of these results: more CoA would increase the turnover of acyl groups. In hyperthyroidism, a similar increase in liver CoA levels has been observed (5). Brady *et al.* (6) found that increased availability of free CoASH increased the oxidation of fatty acids by homogenates of liver. On the other hand, exposure to cold diminished the acetylating capacity of the rat (7). Clearly, it is not possible at present to give an integrated picture of the role of CoA in the processes of adaptation.

REFERENCES

1. WEBER, G. *Rev. Canad. Biol.* 18: 245, 1959.
2. CAMPBELL, J., G. R. GREEN AND H. SOCOL. *Canad. J. Biochem. & Physiol.* 38: 171, 1960.
3. KAPLAN, N. O. AND F. LIPMANN. *J. Biol. Chem.* 174: 37, 1948.
4. TABOR, H., A. H. MEHLER AND E. R. STADTMAN. *J. Biol. Chem.* 204: 127, 1953.
5. TABACHNICK, I. I. A. AND D. D. BONNYCASTLE. *J. Biol. Chem.* 207: 757, 1954.
6. BRADY, R. O., A. MAMOON AND E. R. STADTMAN. *J. Biol. Chem.* 222: 795, 1956.
7. CAMPBELL, J., G. R. GREEN, E. SCHÖNBAUM AND H. SOCOL. *Canad. J. Biochem. & Physiol.* 38: 175, 1960.

Influence of cold exposure on electrolyte metabolism

D. G. BAKER

C. H. Best Institute, Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada

BAKER, D. G. *Influence of cold exposure on electrolyte metabolism.* Fed. Proc. 19, Suppl. 5: 125–130. 1960.—The influence of exposure to cold on electrolyte metabolism has been discussed under two headings: first, the early changes, and second, those responses which are elicited only with prolonged exposure. The early response is characterized by a hemoconcentration of brief duration and, in man, a pronounced diuresis. The concentrations of plasma electrolytes remain relatively unaltered except for an increase in plasma potassium and probably magnesium. After prolonged exposure to cold there is a disappearance or even a reversal of the early changes. Body water and blood volume increase. The total water content of muscle is decreased while the chloride space is increased. The concentrations of potassium and chloride in the plasma remain in the normal range while the sodium concentration is elevated.

I WAS GREATLY HONORED to receive an invitation to give a paper in the Cold Symposium. The pleasure of my acceptance arises largely from the fact that I shall certainly learn a great deal from your discussions. In

slight recompense for this privilege I shall try to give you an account of some current problems in electrolyte metabolism and to present some recent findings for your discussion and criticism.

As Bass and Henschel (1) have pointed out in their excellent review, many organisms are able to tolerate adverse environmental temperatures by appropriate alterations in their water and electrolyte composition. While this may be accomplished by modification of solute concentrations in many of the poikilotherms, the responses of the homeotherms, especially the higher mammals, are more subtle and the mechanisms often obscure. It is to these latter problems that I would like to direct your attention today.

The effects of prolonged exposure to cold may be conveniently discussed under two headings. First, a brief comment on the early changes, that is to say, from several minutes to several days of continuous exposure, and second, those responses which are elicited only with prolonged exposure. Presumably, these develop as part of the organism's process of acclimatization and are the primary concern of this symposium.

EARLY RESPONSES

Among the early responses observed when man is moved abruptly to an ambient temperature below that to which he has become accustomed have been changes in the volume and composition of the blood (2–6). Decreases in plasma volume of up to 15% have been reported, the amount of change depending on the experimental conditions employed. Total blood volume, however, probably undergoes a much smaller decrease (7), which is characteristically accompanied by an increase in the concentration of plasma proteins, hemoglobin and packed cell volume (8). These changes progress over several days of exposure and are usually thought of as indicative of hemoconcentration. Although prominent when human subjects are studied, hemoconcentration occurs to a much lesser degree when small experimental animals are exposed to cold (9–11). Figure 1 illustrates this almost complete lack of effect in the case of a rat exposed to a temperature of 2°C.

The plasma concentration of chloride remained unaltered in most human (12) and animal (9) studies. Where sodium concentrations were measured, both increased (9) and decreased (12, 13) values have been reported. The intracellular concentration of chloride in the erythrocytes of rats exposed to cold for 24 hours was found to decrease below control values (14). Plasma potassium concentrations show an early increase reaching maximum values shortly after exposure to cold and thereafter return to pre-exposure values (9, 15, 16). Figure 2 shows the constancy of the chloride concentration, the early potassium rise and the elevated sodium concentration. Recent work done in Platner's laboratory (17) indicates that there was an early increase in serum magnesium reaching a maximum in about 10 days (an increase from 2.3 mg% to 3.1 mg%) followed by a return to normal over the next 20 days. Concentrations in the liver, heart and skeletal muscles follow a similar pattern of change with time.

These blood changes may be accompanied by a modification of other body fluids. A decrease in total thiocyanate space has been observed in adult males (12) on initial exposure to mild cold in a temperature controlled room. This was not confirmed by Stein *et al.* (18), possibly because of altered experimental conditions.

The decreases in plasma volume and body water, together with the fact that there is no evidence for water retention in any of the major body 'spaces,' would lead one to predict increased water excretion. Spealman *et al.* (19) reported a negative water balance in human subjects during several days exposure to cold. The diuresis which occurs as an early response to cold exposure is, in fact, a common experience (20) in humans though again less prominent in animals (21). The severity and duration of the diuresis is variable, lasting from a few hours to several days (3, 6, 20, 22) and seems to correlate with the reduced body water content (23). Work by Adolph and Molnar (6) showed that the diuresis was markedly influenced by posture, being greatest in the recumbent position. The mechanism of these changes has been investigated by Bader *et al.* (22) who found that exercise also inhibited cold

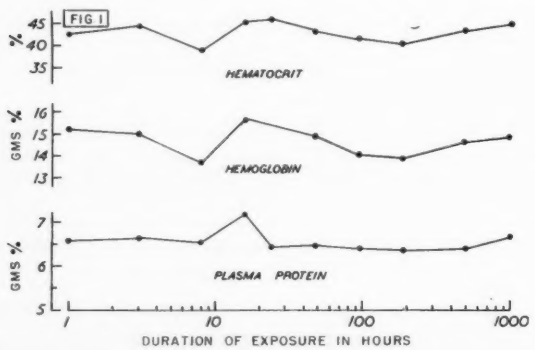


FIG. 1. Certain blood components during exposure to cold of 2°C.

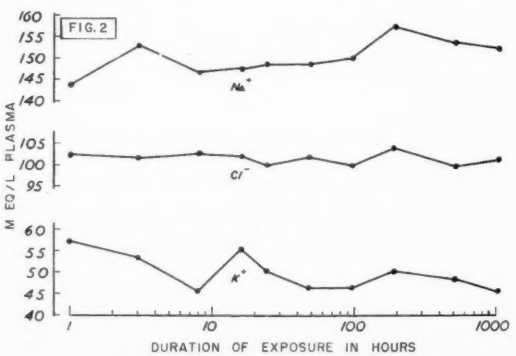
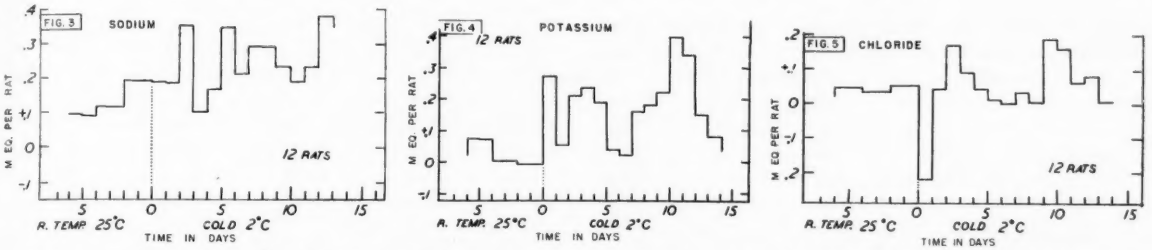


FIG. 2. Plasma electrolytes during exposure to cold of 2°C.



FIGS. 3–5. Sodium balance (fig. 3), potassium balance (fig. 4) and chloride balance (fig. 5) expressed as average number of mEq lost (−) or gained (+) per day per rat. Exposure to cold started on day 0 and the periods of time before or after exposure are referred to the zero time. Each horizontal segment gives the time period for which the indicated balance holds.

diuresis. In their subjects, renal plasma flow was unchanged in the cold; however, the U/P ratio and the chloride excretion were interpreted as an indication of decreased tubular reabsorption of water. Cold diuresis could be completely inhibited by a dose of 0.5 μg/kg/hr of Pitressin and diminished by as little as 0.1 μg. It would appear therefore that cold diuresis is regulated by the posterior pituitary gland. Species differences, however, may be considerable (21). The problem of cold diuresis was studied by J. F. Manery, J. S. Barlow and J. LeBlank (unpublished observations, 1951), using servicemen at the Defence Research Northern Laboratory, Fort Churchill, Manitoba. No simple description of electrolyte excretion was obtained, for although the urinary concentrations of potassium, sodium and chloride were somewhat reduced, the urine volume was increased. The authors observed that chloride excretion exceeded sodium excretion. Total electrolyte excretion was less than would have been expected on the basis of the water loss during the period of diuresis. The response was, therefore, more like a water diuresis than the elimination of excess plasma ultrafiltrate. Diuresis is not an obligatory reaction on exposure to cold but depends in large measure on the state of hydration (24). Caution must be exercised in the interpretation of electrolyte excretion when 'intake' and 'balance' data are not available.

Total balance studies with respect to sodium, potassium and chloride have been done on rats exposed to an environmental temperature of 2 °C by Baker and Sellers (9). Figure 3 shows an early sodium retention and figure 4, a small positive potassium balance. Figure 5 shows a transient chloride loss during the 1st day of exposure, and thereafter a return to the normal balance pattern. Normal balance with respect to these electrolytes was attained by the 3rd week of exposure. Chinn *et al.* (25) have also observed sodium retention in rats exposed to cold. Stein *et al.* (18) observed an initial negative chloride balance when using human test subjects exposed intermittently to cold.

PROLONGED EXPOSURE

The preceding remarks referred to some of the early changes in the body fluids following exposure to cold. Of more interest to this Symposium are those changes which accompany the acclimatization process and which might be considered as physiological modifications suited to the new demands on the organism's mechanisms for homeostasis. To a large extent the early responses are transient and may disappear or even be reversed as a result of continuous exposure.

In the course of his studies on acclimatization to cold, Meehan (26) noted that Eskimos, who, he felt, were acclimatized to cold, had higher blood volumes per kilogram of body weight than either whites or Negroes. In their extensive studies Brown and his colleagues (27–30) reported that the blood and plasma volumes of Eskimos were higher than those found in white subjects. In their Eskimo subjects a small decrease in blood volume developed during the summer months, which was interpreted as evidence for the temperature dependency of the blood volume. Although the number of subjects used in these studies was small and the validity of the assumption that the Eskimo is fully acclimatized to cold could be criticized (31), animal experiments tend to confirm the results. Deb and Hart (10) found that the blood volume, plasma volume and total body water content in rats exposed for 5 weeks to an ambient temperature of 6 °C was significantly higher than in rats living in an environment with a temperature of 30 °C. Baker and Sellers (9) observed similar increases in body water, blood and plasma volumes of rats after 45 days of exposure to a temperature of 2 °C. Under the experimental regimen of this study the rats exposed to cold gained weight at a slower rate than their littermate controls at 25 °C. The data from the cold-exposed rats were therefore compared with those obtained from 'weight' controls as well as to those from 'age' controls; the increases in body water, blood or plasma volume were not significant. It is possible that the younger rats constituting the 'weight' controls had a larger proportion of their body weight as lean body mass than the older weight controls. Table 1 summarizes the data.

In rats exposed to cold (0°–2 °C) for 7 weeks, the total water content of the skin was increased (32) due to an increase in the chloride 'space' (table 2). The total water content of the superficial muscles from these same rats decreased though the chloride space increased, indicating a relative cellular dehydration. Care must be exercised in discussing the chemical composition of skin since it is a complex organ containing many types of

TABLE 1. *Body Fluids During Exposure to Cold*

Treatment	No. of Rats	Aver. B.Wt.	Plasma Vol.		Whole-Blood Vol.			Body Water
		gm	*ml/100 gm b.wt.*	*ml/100 gm b.wa.*	*ml/100 gm b.wt.*	*ml/100 gm b.wa.*	*ml/100 gm d.wt.*	%
Controls for (A) & (B)	10	208	4.25	6.27	7.67	11.33	24.06	67.4
(A) 12 hr. in cold	14	216	4.23	6.52	7.60	11.82	22.11	64.9
(B) 24 hr. in cold	10	206	4.12	6.21	7.46	11.28	22.31	66.0
Age controls for (C)	12	276	3.86	6.39	7.11	11.74	18.03	59.7
Wt. controls for (C)	11	224	4.20	6.55	7.82	12.16	22.19	64.5
(C) 45 days in cold	14	225	4.75*	7.34*	8.63*	13.36*†	24.58*†	64.6*†

B. wt. = body weight; *b. wa.* = body water; *d. wt.* = dry carcass weight. * 'Cold-exposed' values which differ significantly ($P < .05$) from corresponding control values. † 'Treated' values which differ significantly only from age control.

TABLE 2. *Change of Water Content in Skin and Muscles of Cold-Exposed Rats*

Test		2°C	25°C
$(Na)_T$ *mEq/kg*	Skin	66.42±0.98	64.23±1.24
	Muscle	28.15±1.09	26.93±0.94
$(Cl)_T$ *mEq/kg*	Skin	54.89±4.72	52.38±4.21
	Muscle	15.13±2.82	12.56±0.60
$(H_2O)_E^{Cl}$ *gm/kg*	Skin	563.2±4.8	549.0±3.5*
	Muscle	156.5±2.9	130.3±6.2*
$(H_2O)_T$ *gm/kg*	Skin	620.9±3.1	602.1±2.5*
	Muscle	750.5±2.6	759.9±2.7*

* Statistically significant difference ($P < .05$).

tissue. In order to 'define' the tissue used as skin by Baker and Sellers, attention is drawn to fig. 6. This is a photomicrograph of an H and E section from the skin of a rat exposed to cold.

Intracellular sodium was also decreased in Baker's animals. Deb and Hart (10), on the other hand, observed no change from control values in total extracellular water (Na^{22} space) of rats exposed to 6°C for 5 weeks, but found intracellular water expresses per 100 gm of body weight to be increased. The discrepency between these observations and those of Baker might lie in the fact that Baker selected superficial muscles. Since the temperature of this tissue was below that of the main body mass, difference in fluid distribution might be expected (33).

Although only a subjective impression, an observation by Frazier (34), who was the medical officer of the U. S. Antarctic Service Expedition and spent a year in Little America III, is of interest. He found that men who had spent considerable time outside had a greater resistance to frostbite than those whose occupations kept them inside. He commented on apparent dryness of the skin of the outdoor group and considered that dehydration was partially responsible for their resistance to cold injury. Possibly the low temperature used in Baker's study stimulated a similar reaction.

Prolonged exposure to cold does not change the plasma electrolyte composition except for sodium, which is slightly elevated (9, 13).

DISCUSSION

It is always desirable to conclude a discussion of this sort by a summation of the facts and an interpretation that integrates the material into a pattern in which cause, effect and mechanism become recognizable. This I am

FIG. 6. Photomicrograph of a representative piece of skin from a rat acclimatized to cold. Hematoxylin and Eosin, × 35.

unable to do, for though the available information is extensive, our knowledge is far from complete. Many interesting observations are not amenable to interpretation owing to the lack of adequate control. The importance of age, sex, nutritional state and so on may all act to some extent as modifying factors on the response to cold.

In the early response to cold the transient hemoconcentration has been the object of considerable speculation (1). The reduction in plasma volume could conceivably be of value in accommodating the blood volume to the reduced vascular bed. However, the ability of the splanchnic area, lungs and liver to act as blood reservoirs militates against this.

Immediately on exposure to cold metabolic rate must be increased to compensate for the accelerated heat loss. In the rat exposed to a cold of 1.5°C, for example, the increase is expressed by more than a twofold increase in oxygen consumption (35). Hemoconcentration would effectively increase the oxygen-carrying capacity of the blood until circulatory and respiratory adjustments provide a more permanent compensation. The elevated metabolic rate also increases the production of carbon dioxide and other acid metabolites. Perhaps maintaining acid-base balance in the acute period is facilitated by the decreased ratio of sodium to chloride excreted. Also in the realm of speculation, would the sudden increase in metabolic activity, presumably in muscle, liberate enough potassium to account for the early rise in plasma concentration? Work by Fenn and Haege (36) and others (37) supports this thesis. The role of the adrenal gland in this response is probably secondary in that it facilitates the return of the plasma potassium concentration to normal values (16).

The increased metabolic activity of the tissues of small animals after prolonged exposure to cold (38–41) is facilitated by an increase in the size of the vascular bed (42). The increase in blood volume is probably a part of this same response.

The effect of cold on the tissue electrolyte composition is more difficult to rationalize. Reader (43) found the thermal conductivity of tissues dependent on the water content. A generalized dehydration of peripheral tissues would thus tend to conserve body heat. Conversely the slowed heat transfer would make the peripheral tissues more prone to cold injury. An increase in extracellular fluid accompanied by a decrease in intracellular fluid might provide for an optimum tolerance to cold.

The mechanism and control of these water and electrolyte shifts is at the moment largely speculative. Nervous mechanisms (1, 44), central and peripheral, undoubtedly play an important role. Subsequent papers will deal with these problems in detail. The tissue temperature itself is an important factor in controlling tissue electrolyte composition (18, 45). In a recent discussion, Dr. Fremont-Smith suggested that some, if not all, of the changes in the tissue electrolyte composition just mentioned could be accounted for by thermodynamic considerations based on the temperature gradients imposed by the cold. This approach might well lead to the solution of one of the most difficult problems in the field.

REFERENCES

1. Bass, D. E. and A. Henschel. *Physiol. Rev.* 36: 128, 1956.
2. Barcroft, J., C. A. Bingert et al. *Phil. Trans. Roy. Soc. London. Ser. B* 211: 351, 1922.
3. Bazett, H. C., F. W. Sunderman, J. Doupe and J. C. Scott. *Am. J. Physiol.* 129: 69, 1940.
4. Burton, A. C., J. C. Scott, B. McLone and H. C. Bazett. *Am. J. Physiol.* 129: 84, 1940.
5. Scott, J. C., H. C. Bazett and G. C. Mackie. *Am. J. Physiol.* 129: 102, 1940.
6. Adolph, E. F. and G. W. Molnar. *Am. J. Physiol.* 146: 507, 1946.
7. Axelrod, D. R. and D. E. Bass. *Am. J. Physiol.* 186: 31, 1956.
8. Spealman, R. C., M. Newton and R. L. Post. *Am. J. Physiol.* 150: 628, 1947.
9. Baker, D. G. and E. A. Sellers. *Canad. J. Biochem. & Physiol.* 35: 631, 1957.
10. Deb, C. and J. S. Hart. *Canad. J. Bioch. & Physiol.* 34: 959, 1956.
11. Stulken, D. E. and W. A. Hiestand. *Proc. Soc. Exper. Biol. & Med.* 86: 253, 1954.
12. Conley, C. L. and J. L. Nickerson. *Am. J. Physiol.* 143: 373, 1945.
13. Barlow, J. S. D.R.B. Northern Lab., DRNL Technical Paper 13, Oct., 1954.
14. Karady, S., H. Selye and J. S. L. Browne. *J. Biol. Chem.* 131: 717, 1939.
15. Quinn, M., D. E. Bass and R. C. Kleeman. *Proc. Soc. Exper. Biol. & Med.* 83: 660, 1953.
16. Booker, W. M., R. L. Hayes, F. D. DaCosta, W. Jones, R. Hill and P. Titus. *Fed. Proc.* 11: 15, 1952.
17. Neubeiser, R. E. *A Study of Magnesium and Body Fluids of the Rat During Cold Acclimation* (Thesis) Columbia: University of Missouri School of Medicine, June 1958.
18. Stein, H. J., J. W. Eliot and R. A. Bader. *J. Appl. Physiol.* 1: 575, 1949.
19. Spealman, R. C., W. Yamamato, E. W. Bixby and M. Newton. *Am. J. Physiol.* 152: 233, 1948.
20. Gibson, A. A. *Quart. J. Med.* 3: 52, 1909.
21. Nungesser, W. C. *Fed. Proc.* 14: 108, 1955.
22. Bader, R. A., J. W. Eliot and D. E. Bass. *J. Appl. Physiol.* 4: 649, 1952.
23. Eliot, J. W., R. A. Bader and D. E. Bass. *Fed. Proc.* 8: 41, 1949.
24. Bass, D. E. *Fed. Proc.* 13: 8, 1954.
25. Chinn, H. J., F. W. Oberst, B. Nyman and K. Fenton. Project 21-23-027, USAF Randolph Field, Tex. Sept. 1950.
26. Meehan, J. P. *Am. J. Physiol.* 179: 657, 1954.
27. Baugh, C. W., G. S. Bird, G. M. Brown, C. S. Lennox and R. E. Semple. *J. Physiol.* 140: 347, 1958.
28. Brown, G. M., G. S. Bird, S. J. Boag, L. M. Boag, J. D. Delahaye, J. E. Green, J. D. Hatcher and J. Page. *Circulation* 9: 813, 1954.
29. Brown, G. M., G. S. Bird, D. J. Delahaye, J. E. Green, J. D. Hatcher and J. Page. *Canad. M.A.J.* 70: 258, 1954.
30. Brown, G. M., G. S. Bird, L. B. Boag, J. D. Delahaye, J. E. Green, J. D. Hatcher and J. Page. *Metabolism* 3: 247, 1954.
31. Stefansson, V. *The Friendly Arctic.* New York: Macmillan, 1921.
32. Baker, D. G. *Canad. J. Biochem. & Physiol.* In press.
33. Aebi, H. *Biochem. J.* 54: Proc. p. xi, 1953.
34. Frazier, G. *Proc. Am. Phil. Soc.* 89: 249, 1945.

35. Sellers, E. A. and S. S. You. *Am. J. Physiol.* 163: 81, 1950.
36. Fenn, W. O. and L. F. Haege. *J. Biol. Chem.* 136: 87, 1940.
37. Flock, E. V. and J. L. Bollman. *J. Biol. Chem.* 136: 469, 1950.
38. Weiss, A. K. *Am. J. Physiol.* 177: 201, 1954.
39. You, R. W. and A. E. Sellers. *Endocrinology* 49: 374, 1951.
40. Weiss, A. K. *Am. J. Physiol.* 188: 430, 1957.
41. Weiss, A. W. *Am. J. Physiol.* 196: 913, 1959.
42. Heroux, O. and J. St. Pierre. *Am. J. Physiol.* 188: 163, 1957.
43. Reader, S. R. *Clin. Sc.* 11: 1, 1952.
44. Hertzmann, A. B. *Ann. Rev. Physiol.* 17: 79, 1953.
45. Hogkin, A. L. *Biol. Revs. Cambridge Phil. Soc.* 26: 339, 1951.

Electrolytes in acclimation to cold

W. S. PLATNER

Department of Physiology, University of Missouri School of Medicine, Columbia, Missouri

Platner, W. S. *Electrolytes in acclimation to cold.* Fed. Proc. 19, Suppl. 5: 130–131. 1960.—The changes in the electrolyte content of tissues and serum of animals exposed to cold is discussed in terms of the effect of hormones upon the electrolyte balance. The independent variations of concentrations of ions under differing conditions of stress would indicate different mechanism of control. Work by the author has shown that the magnesium content of serum and heart and muscle tissue increased 37% in rats exposed to 4.5°C for 40 days.

Prolonged exposure to cold of warm-blooded animals imparts various protective modifications in many physiological processes. These acquired, reversible responses may be termed expressions of acclimation and discretely used as measures thereof. While many of these modifications which occur in an organism are of debatable value as primary causative instruments of the acclimatization process, they nevertheless are salient factors in the determination of the existence of the acclimated state. Now we should try to define the mechanisms involved in the movement of ions in acclimation by asking ourselves these questions:

1) Are these movements independent of hormone effects? Are they independent of water shifts?

2) Are the movements the result of physical forces such as diffusion or osmotic pressure gradients which can account for the ion movements across cell membranes?

3) Is the so-called 'pump-mechanism' a possibility? In the case of sodium one would have to postulate from the work described by Dr. Baker that the efficiency of the pump is first increased in the early stages of the acclimation process since sodium levels rise; later, as the animal approaches the acclimated state and becomes temperature adjusted, one would have to postulate that it operates at a lower temperature level and is less efficient since sodium falls. This could explain the response of sodium to cold acclimation. However, if one postulates a sodium pump, then why not a magnesium pump, a chloride pump, etc.? Such a postulate does not explain how the pump is driven or what turns it on or off.

The fact that ions such as sodium, potassium, chloride and magnesium vary independently of each other would be an argument in favor of some separate controlling mechanism for each ion. One is tempted to speculate that perhaps sodium retention in early stages of acclimation is due to an over active adrenal. Da Costa *et al.* (1) reported a lag between the onset of stress and the changes in the electrolytes that should follow adrenal hormone release. This would imply that during the early stages of acclimation not all ion changes coincide with adrenal activity and suggest the involvement of other factors.

The observation of Katsh *et al.* (2) on the failure of the hypophysis to attain normal ascorbic acid levels until after 10 days of cold exposure suggests that, although the adrenals are hyperactive at this time, the animal is in reality suffering from a modified form of hormonal insufficiency. Katsh also reported a rise in muscle magnesium following adrenalectomy which would argue for an unbalanced hormone system.

Whatever the mechanisms, the results are clear: Na^+, K^+, Cl^- and Mg^{++} levels rise early in acclimation, paralleling the initial rise in metabolism. As the animal becomes adjusted we see a new metabolic state and a readjustment in electrolyte balance.

Work done in our laboratory by Mr. Neubeiser (3) shows that on exposure of the rat to cold ($4.5° \pm 1.5°C$) for prolonged periods (40 days), the serum magnesium rises some 37%. This figure becomes considerably higher when corrected for dilution due to an increased blood volume. Our first smapling time was after 10 days of exposure, and therefore this rise may have occurred sooner. Thereafter, the magnesium level of serum slowly

declines, but still remains elevated after 40 days. We asked ourselves where this magnesium came from. Analysis of skeletal muscle and heart showed an 11% increase in magnesium content of these tissues coincident with the rise in serum magnesium.

Fenn and Haege (4) reported that muscle cells can release or absorb magnesium depending on the concentration in the serum. This would only establish equilibrium, but could not explain the source of serum magnesium increase. Perhaps bone or skin supplies the elevated magnesium levels, since they are rich in magnesium. However, these tissues still remain to be analyzed in cold acclimation.

The ions mentioned here have been those most frequently reported in the literature, but practically no work has been done with Ca^{++}, Mn^{++}, Zn^{++}, Cu^{++}, SO_4^{--}, Fe^{+++}, PO_4^{---}, Co^{++}, etc. These ions are important in various biochemical processes. Much still remains to be done before we can talk intelligently about the total electrolyte picture in cold acclimation.

REFERENCES

1. Da Costa, F. M., W. M. Booker, A. H. Maloney, W. M. Jones and C. Froix. *Fed. Proc.* 12: 30, 1953.
2. Katsh, S., G. F. Katsh and P. Osher. *Am. J. Physiol.* 178: 457, 1954.
3. Neubeiser, R. E. *A Study of Magnesium and Body Fluids of the Rat During Cold Acclimation* (Thesis). Columbia: University of Missouri School of Medicine, June 1958.
4. Fenn, W. D. and L. F. Haege. *J. Cell. & Comp. Physiol.* 19: 37, 1942.

Discussion

R. W. BRAUER, F. DEPOCAS, J. P. HANNON, D. G. BAKER, O. HEROUX, M. F. MORALES, S. A. D'ANGELO, I. L. TRAPANI, R. S. GORDON, JR., R. E. SMITH, E. J. MASORO, A. K. WEISS

Dr. Brauer: While listening to the last two papers, it struck me that they afford a nice example of the difference between the hypothermic and the cold-adapted animal. Dr. Scholander so far has kept quiet about a point that he made some years ago, namely, that you are not going to have cold acclimatization without some regional hypothermia, at least for a while. It may well be appropriate to compare these papers, which talk about changes in carbohydrate metabolism in the cold-acclimatized animal, with the information about corresponding changes in the hypothermic animal given by Dr. Mikailovic this morning. With respect to the cold-acclimatized animal the general consensus seems to be that there is an increased net rate of glucose metabolism; in the case of hyperthermia we have to work a little harder to prove anything about carbohydrate metabolism. The evidence seems to be reasonably consistent, though, that the hypothermic animal does not metabolize carbohydrate as readily as the normothermic animal. In all these situations it is important to establish whether or not there are shifts in the distribution space of the test carbohydrate. This is definitely changed in hypothermia. I believe that any such changes could also affect the measurements Dr. Depocas has presented here, unless he has additional data which permit a separation of variables. The questions I would ask are: How good is our information on the volume of fluid through which glucose is distributed? What is the rate of disappearance of the carbohydrate from the blood, or the glucose concentrations in the key tissues?

A second point that intrigued me in listening to Dr. Hannon's paper is the phenomenon that we do see apparent differences in liver metabolism in these cold-acclimatizing animals. If you recall, livers in cold-adapted rats have been found to increase rather considerably in size. I have not seen in the literature, and I lack from my own laboratory, the data that would allow me to tell whether this increase in liver mass represents a hypertrophy or hyperplasia, or whether it represents an accumulation of fluid as it would in the hypothermic animal. Certainly, if we were dealing with livers that were growing actively, I know from my own experience with liver regeneration that there are considerable changes in metabolism as well as in enzyme content of the tissue. I wonder if such changes may be at all relevant to the phenomena that you are looking at.

The next point I am delighted to hear answered, and one that makes a nice contrast with the hypothermia situation, is found in the data that Dr. Depocas presented concerning the preferential fat utilization during thermogenesis. This has been a vexing question in dealing with the acute hypothermia situation with its apparent decrease in respiratory quotient; some have thought the decrease indicated preferential utilization, while others have suggested that it might represent a change in gaseous metabolism to give a false lowering of the RQ. In fact, there is some evidence favoring this latter point of view in hypothermia. I am very happy to see this situation settled conclusively for cold-acclimatized animals.

In viewing many of these results, I would like to raise one word of caution. When we talk about an organ such as the liver, we are prone to take a whole organ and toss it into a homogenizer and perform our analyses on the resulting mash.

To the histologist this is not always a happy situation. For instance, you cannot take an animal and make it violently hyperthyroid, and then toss pieces of it into a Waring Blendor to disguise and grind up the evidence, and do so with any assurance that you are grinding up mostly viable tissue. A very sizable portion, probably about 10 or 15% of that tissue, may be dead or dying; this is a well-known phenomenon in the case of the liver. Some of our British colleagues have done a very nice job of pointing out that under these conditions different enzyme systems lose their activities at different rates so that you may get quite diverse metabolic profiles. I wonder whether such tissue heterogeneity should not be considered as another source of confusion in some of the experimental situations we are talking about.

DR. DEPOCAS: I would just like to give direct answers to the questions on the volumes of distribution of glucose. These, of course, have been measured from the values of pool size and the concentration, and they come out very close to one another. Looking at the more complete data from which the last slide I showed was abstracted, the glucose spaces were larger in the cold-acclimated rats, which is in accordance with previous measurements of extracellular fluid volumes in warm and cold-acclimated rats made by Dearborn Hart, who found that there was a significant difference in the same direction as that found with this method. So the glucose spaces are different, but I do not think that the other data are very much affected by this.

DR. HANNON: I would like to answer Dr. Brauer's question concerning the composition of the liver in the cold-acclimatized animal. We have done gross chemical analyses of these livers in the 1-month cold-acclimatized animals (1) and we have observed the relative increase in liver size reported by others. Our data indicate that this size increase is due to actual tissue growth. For instance, we find no difference in protein, ash or water content per unit weight; we do, however, find differences in such things as the glycogen content, which is slightly but significantly lower; lipid content which is slightly increased; and phospholipid content which is markedly increased. The foregoing information was obtained in the 1-month cold-acclimatized rat maintained on a stock laboratory diet. A slightly different state of affairs has been observed under different dietary or exposure conditions (2). In all cases, however, the increase in relative liver mass is due to an actual tissue growth and not to an accumulation of inert material such as water.

DR. BRAUER: I have occasionally watched rats being cold-acclimatized, and all of you of course have done this. Even with careful handling, those rats, as far as I can tell, are never the sort of relaxed, butterball type of rat that I am accustomed to dealing with in my laboratory. A fact that keeps puzzling me, and perhaps some of you can explain it, is that as a result of shivering these rats acquire a phenomenally good type of physical conditioning. In all the experiments, the control animal that one conventionally uses is the butterball, relaxed kind of rat that has lived a sheltered life. It may be that this is quite proper, but I would very much like to hear whether or not anybody here has considered using as a control in their experiments rats that have been put through a rather vigorous physical conditioning schedule that has not involved exposure to cold.

DR. BAKER: May I reply to the point raised by Dr. Brauer. If you handle these animals frequently during the acclimatization periods, for example, just weighing them daily, you will find they become as gentle as your other animals. It has been my experience that daily handling will significantly increase the number of rats surviving prolonged exposure to cold. This is most marked when you wish to acclimatize young rats.

Dr. Hannon, did you measure the enzyme activity at the *in vivo* temperature of these muscles? In rats acclimatized to cold (1°C), the temperature of the superficial muscles is 4° to 5°C below the temperature of the same tissues in nonacclimatized rats in an environment with a temperature of 25°C. Similarly the liver temperature is 1°C higher than that of the room temperature control. I wonder if you would have found significant differences in enzyme activity if the measurements had been made at the *in vivo* temperature of the tissues?

DR. HANNON: These were all measured at 30°C.

DR. HEROUX: In answer to the question about the temperature at which measurements are made, I would like to say that we did some *in vitro* respiratory measurements on the ear skin at the *in vivo* temperature at which the ear skin is maintained in rats kept at 6°C (3). At 18°C the respiratory rate was so slow that we could not detect any difference between the skins of the rats acclimated to 30°C and the skins of the 6°C acclimated rats. When the measurements were done at 37°C, however, the respiratory rate was significantly higher in the cold-acclimated rats' skins than in the warm rats' skins. At 27.5°C the difference between the two groups was still significant but much less than at 37°C. This means, we think, that in carrying on *in vitro* studies, it is preferable to make the measurements at 30°C or 37°C than at the *in vivo* temperature of the tissue since at those high temperatures it might be possible to detect a small difference between two groups that could be missed at a colder temperature.

I would like to make one more comment which has some bearing on Dr. Hannon's results. I have objected to the habit we all have of expressing our results per unit weight or per 100 gm of body weight because the cold-acclimated animals are growing at a slower rate than the controls (4). I think that this procedure is a mistake and that it is quite time we realized it, because when we express our results on a percentage basis we assume that there is a direct proportion between the variable and the body weight, which is not true most of the time. For example, if we want to compare the liver weight of warm- and cold-acclimated animals which are of a different body weight, the only way of differentiating between the specific effect of cold on the liver and the unspecific effect due to a different general growth is to use the least square method to establish the relation that exists between the liver and the body weight and then use the equation to calculate the weight of the liver for a common body weight. A percentage weight for a variable, in the absence of a correlation between the variable and the total body weight, is indeed meaningless. This, of course, does not only apply to organ weights but also to any variable which is a function of another one, as for example, enzyme concentration in an organ. When the enzyme activities or concentration in the organs of two different groups are compared on a percentage basis (to eliminate the difference in weight of the organs), it is assumed that the enzyme activity is directly proportional to the size of the organ. When there are not enough data to establish a significant relationship between two variables, it is better to express the results on an absolute basis rather than on a percentage basis. The latter assumes correlations that may not exist and could lead to very serious errors.

DR. MORALES: I have two short questions for Dr. Hannon. One of the major results of the last two years work in intermediary metabolism has been that the reversal of glycogenolysis does not go over phosphorylase but over the UDPG system. This is one of the great results from Professor LeLoir's

laboratory and now has been confirmed in muscle by Lipman. I wonder, then, if perhaps the UDPG system may be a place to look, rather than for changes in phosphorylase. And the second question is, when you say, and when people tomorrow will say, that the enzyme activity is different in acclimatized and nonacclimatized animals, exactly what does that mean? Do you pull out the enzyme pure, measure the V_{max}, or do you have it in a Brei where all the other paths are blocked and you measure the activity in question? Or is it in a sequence and you only dump in maximum substrate? It would be an interesting question to determine whether the enzyme itself is changed when its activity is different in two situations, or whether its amount is changed, or whether just its position in a pathway is modified.

DR. HANNON: We have studied liver oxidative enzyme activities in exercised rats and we get quite the opposite results than obtained in the cold-exposed animals, i.e. they go down rather than up (unpublished observations). With regard to the lowered rate of cold-exposed rats, there has often been speculation that this is due to an inability of these animals to eat enough food to maintain both homeothermy and normal growth. In other words, cold-exposed rats might be considered as semistarved. In experiments currently being conducted, we are testing this by adding a control group that is pair-fed for a weight gain equivalent to that shown by cold-exposed animals. The results obtained up to this time indicate that cold exposure and semistarvation in most cases lead to quite different effects, at least at the glycolytic level.

DR. D'ANGELO: Some of the physiologic changes occurring in cold acclimation also occur in other environmental conditions, for example, at high altitudes. In this connection I direct a general question to the biochemists. Let us assume that changes have been induced in the animal by an environmental stimulus other than cold but that the changes are nevertheless in the same direction. Has any advantage been conferred on that animal in terms of subsequent cold-acclimation—either biologically or chemically speaking?

DR. BAKER: First of all, I would like to congratulate Dr. Trapani on his excellent work and fine presentation. Dr. Trapani, could the inhibited antibody production you have observed be related to an increased secretion of adrenal cortical hormones?

Have you considered the possibility that the accelerated turnover rate was really a reflection of the general increase in metabolic activity of all tissues in the animal exposed to cold? Can the turnover rate be increased by any other process that increased the over-all metabolic rate?

Recently we (D. G. Baker, and E. A. Sellers, unpublished observations) have become concerned with the spectrum of plasma proteins in the rat exposed to cold. Using electrophoresis on starch gels we have observed the presence of a plasma protein component having a similar electrophoretic mobility to the 'transferrin' compenent of human serum. Have you observed any similar proteins which seem to develop in response to prolonged exposure to cold?

DR. TRAPANI: No, we have not encountered any of these abnormal proteins in rabbits. It is possible, of course, that the particular protein which you have found in the serum of the cold-exposed rat may also be present in the serum of other species, but in too low a concentration to be distinguished electrophoretically from what is ordinarily accepted as 'normal' for that species. The resolution of the serum into its respective electrophoretic components depends in part upon the sensitivity of the method used and also upon the choice of buffer. With different buffer systems it may be possible to pick up these other types of proteins.

I think that the question of a relationship between protein turnover and metabolic rate can be answered in the affirmative. In the case of the cold-exposed animal the influence of the thyroid, at least, appears to be implicated. To test this idea we undertook the experiments on the influence of the thyroid under experimental conditions similar to those employed in the cold-exposure study. The data we have obtained so far suggest that at least part of the altered response pattern of the cold-exposed rabbit can be attributed to changes in thyroid activity.

The possibility that an apparent delay or inhibition of the antibody response might be due to adrenal cortical influence is something which should be considered. Unfortunately, the literature on this subject is confusing due to the many apparently conflicting reports and makes any answer something less than satisfactory. One must consider, among other things, the antigen-antibody system used, the species of experimental animal, etc. Perhaps I can answer the question partially by mentioning some evidence which we have obtained from the study of a stress other than cold-exposure, namely that of high altitude acclimatization. During the summers of 1958 and 1959 we conducted experiments, similar to those of the cold-exposure studies, at the Barcroft Laboratory (altitude, 12,470 ft.) of the White Mountain High Altitude Research Station, California. I believe that it would not be presumptuous to say that animals acclimatized to this altitude experience stress, with an increase in the secretion of adrenal cortical hormones. In these experiments, the problem was restricted to the study of a BSA vs. anti-BSA system in rabbits. Whether or not a similar result will be found with other systems and with other species of animals remains to be seen. The half life of passively administered homologous antibody in these animals was essentially unchanged from that of sea level controls. Active immunization, however, resulted in levels of circulating antibody which were higher than those in sea level controls and were greater than might be expected on the basis of the decrease in plasma volume which occurs at high altitude. Thus it would seem that in this situation there is an accentuation of the immune response, due in part to adrenal cortical activity, expressed by an increase in circulating antibody.

In any study of this type, it is important to be aware of the concept that the animal is functioning as a complete unit. Even though we might like to consider the thyroid or the adrenal cortex, etc., as separate influences, they are really acting in some integrated fashion, not only in terms of the net result which we measure but also in terms of their relation to each other.

As a final point, even though we make an extrapolation from our immunological studies to protein metabolism in general, this extrapolation is not necessarily justified in all cases; other types of proteins may be handled in a different manner, depending on their activity relative to the host animal.

DR. HANNON: I would like to indicate that we have some data on two other species very similar to those found by Dr. Trapani with rabbits. We have observed in the rat and the Alaskan Husky that plasma protein levels increased during periods of cold exposure. We have also observed an increase in plasma amino-acid nitrogen levels, which would suggest an increased turnover of protein during cold exposure. There also are numerous reports of an increased nitrogen excretion during cold exposure.

DR. TRAPANI: How much of the increased excretion of nitrogen would be due to an increase in food intake?

XUM

DR. HANNON: We do not know this for certain but undoubtedly it accounts for a large part of it. Young and Cook (5) concluded that most of the increase in rats was due to an increase in food intake.

DR. GORDON: It has been reported (6) that alterations in the dietary protein intake affect the turnover rate of serum albumin. In the experiments reported at this session, it seems to me that there is a possibility that the cold-acclimatized animals, consuming greater quantities of diet and therefore more protein, might for that reason alone have shown a greater protein turnover rate.

DR. HANNON: This is probably true, at least to some extent. The animals in the cold box get the same type of ration but perhaps they eat approximately half again as much, but I still do not think that this would account entirely for some of the large differences observed.

DR. BAKER: With regard to this protein turnover, the rat is a rather special case because it excretes protein in its urine, and if the animal has been acclimatized to cold, as time goes on it excretes more and more urine protein. In some of our animals we have taken clean urine right from the bladder which contains about 2% protein. This is a colossal loss to the animal that excretes, say, 18 to 20 cc of urine per day and undoubtedly contributes to some of the accelerated protein turnover in the long-acclimatized animal. We lyophilized this urine and analyzed it with paper electrophoresis: some urines match exactly the protein patterns that exist in the plasma, and except for the very high molecular weight proteins, the same type of protein with the same electrophoretic characteristics appears in the urine as in the plasma.

DR. SMITH: We have made some measurements of creatinine and creatine excretion in rats acclimatized to the cold and controlled against shivering. We find, not unexpectedly, as in the work of Bodansky some years ago, that the creatine excretion levels are increased significantly in cold-acclimated animals and so are creatinine levels, as might be expected from metabolic rate changes.

DR. TRAPANI: As a last commentary, I wish to thank Dr. Smith for inviting me to a symposium like this and permitting me to present material somewhat apart from what we might ordinarily consider as the scope of environmental physiology. I would like to invite the members of the Symposium to consider the use of immunological techniques in physiological studies, and conversely, immunological responses under controlled physiological conditions. This might be termed an immunophysiological approach to certain biological phenomena, and if more of us were to work in the area, this particular field of endeavor would progress a little faster.

DR. MASORO: Dr. Mefferd rather cautiously mentioned that his own data show fat synthesis in the cold-acclimated rat to be normal. One might therefore gain the impression then that his data are in disagreement with those presented today. However, I don't think that the findings are mutually exclusive. We find in our laboratory that many of the changes in liver metabolism induced by cold exposure are not found in the metabolism of extrahepatic tissues. Since it is well known that less than 5% of the fat synthesis occurring in the animal takes place in the liver, it is not surprising that a failure in hepatic lipogenesis might not result in any appreciable reduction in fat synthesis in the intact animal.

I was also very interested in the food intake curves that Dr. Mefferd observed on exposing animals to a cold environment. We have also observed similar food intake curves but find that the shape of the curve was related to the kind of fat in the diet. All of our diets contain 10% fat. One of the following kinds was used: lard, corn oil, hydrogenated vegetable fats or hydrogenated vegetable fats plus polyunsaturated fatty acids. Each fat type changed the time course by which the rat attained maximum food consumption while living at 0° to 2°C.

DR. WEISS: Dr. Mefferd made a plea for standardization of the temperature at which various workers conduct their experiments. This is of course impossible, as Dr. Mefferd realized, and I think we all realize that while there are some desirable features in this idea, it cannot be carried to its successful conclusion. There is, however, an instrument available—I believe it is called a Katathermometer—which measures the rate of cooling of a specific environment or cold box. Now, if we were to have available the cooling rate data of the particular environmental condition in which we expose our experimental subjects, we would be greatly helped in interpreting our own data as well as that of other workers.

DR. BRAUER: I am impressed with the fact that the rat, at least, walks around in his 2° environment with cold feet and cold legs, a fact which I think is pretty well established. I don't have any measurements on muscle but I do have some on cooled livers. If you change the temperature of the perfused liver and measure various fluid compartments and also record continuously the organ weight, you can demonstrate that at 30°C the intracellular compartment has (reversibly) increased by some 6% of the total organ weight compared with the same preparation at 38°C (7). I should imagine that at least 15% of a rat's tissues are at temperatures well below 37°C when in a cold room. Thus, if my liver data are at all applicable to skin and muscle and such, the cold-exposed rat has an excellent excuse for a rather perceptible water retention—in fact almost of the same magnitude as the values you report. An additional source of change in fluid and electrolyte balance in the cold-exposed animal is, of course, the altered metabolic rate. Only when these two fail to account for the observed changes should we have recourse to an appeal to active adaptive or control mechanisms. I wonder whether one can find a way of sifting these several possibilities so as to arrive at an estimate of the importance of active cold acclimation in regard to electrolyte metabolism.

DR. MORALES: If the fraction of cellular energy stores available for work is diminished in favor of dissipation into heat, the cellular pumps might suffer as a result of this shift and the electrolyte pattern would change in the direction of having the pumps depressed; that is to say, sodium would be pumped out less and perhaps as a result of that, potassium would shift in the opposite direction. I would think this might be a pattern to look for with respect to electrolytes.

DR. D'ANGELO: I have a short question directed to Dr. Baker. In addition to the localized shifting in the electrolytes and water due to the temperature gradients, is there any experimental evidence implicating the hormone aldosterone in these processes at low temperatures?

DR. BAKER: I know of no experiments where the response to aldosterone has been tested in the animal acclimatized to cold.

DR. HANNON: In regard to effects of temperature on water movement, a few years ago I did some work with mouse diaphragm (8) that is pertinent here. If you take mouse diaphragm and place it in physiological saline maintained at 0°C, it will increase in weight by about 35% due to the uptake of water. Similar changes have been found by others in other tissues (9). We can conclude, therefore, that lowered temperatures can cause an increase in intracellular water. I think it should be brought out that Conway's group (10) has presented some pretty good evidence that this is due to an increase in intracel-

lular solute concentration at low temperature, tending to pull water in.

DR. BAKER: Yes, it does. This also occurs in isolated tissues as Aebi (11) has shown. *In vivo* studies, however, indicate that this increase in water is extracellular.

I agree with what you say. Many of the changes in tissue electrolyte composition could be explained in part by thermodynamic principles based on the temperature gradients present in the rat exposed to cold. Physiological factors are also important. Unfortunately, we have not yet devised sufficiently ingenious experiments to resolve the relative importance of these mechanisms.

The average subcutaneous temperature of 22 cold-acclimatized rats in an environmental temperature of 2°C was observed to be 34.9°C. On removal to an environmental temperature of 25°C it increased to 35.8°C over an interval of several minutes and thereafter remained unchanged for some time. The deep body temperature of these same rats remained at approximately 39.5°C throughout the observation period. Nonacclimatized rats with deep body temperatures one degree lower nevertheless had subcutaneous temperatures averaging 36.3°C, or one-half a degree higher than those of the cold-acclimatized rats. These data suggest to me that at least three factors influence the temperature gradients across the peripheral tissues. The immediate increase in temperature as the rat was brought from a 2°C to a 25°C environment might be due to a reversal of the cold-induced peripheral vasoconstriction, viz. a direct effect of temperature on the vessels. The later increase suggests that an additional factor, nervous or humoral, was also active in controlling the peripheral vascular tone in the cold-acclimatized rat. A third possibility is that the initial increase in temperature as the animal was removed to the 25°C environment stimulated increased metabolic activity, and hence initiated a further temperature increase.

REFERENCES

1. HANNON, J. P. AND L. N. VAUGHAN. AAL Tech. Rept. 58-19.
2. VAUGHN, D. A., J. P. HANNON AND L. N. VAUGHAN. *Am. J. Physiol.* 194: 441, 1958.
3. HEROUX, O. *Canad. J. Biochem. & Physiol.* 37:1122, 1959.
4. HEROUX, O AND N. T. GRIDGEMAN. *Canad. J. Biochem. & Physiol.* 36: 209, 1957.
5. YOUNG D. R. AND S. F. COOK. *Proc. Soc. Exper. Biol. & Med.* 89: 482, 1955.
6. JEFFAY, H. AND R. J. WINZLER. *J. Biol. Chem.* 231: 111, 1958.
7. BRAUER, R. W., J. J. HOLLOWAY, J. S. KREBS, G. F. LEONG AND H. W. CARROLL. *Ann. New York Acad. Sc.* 80: 395, 1959.
8. HANNON, J. P. AND S. F. COOK. *Am. J. Physiol.* 187: 155, 1956.
9. ROBINSON, J. R. *Biol. Revs. Cambridge Phil. Soc.* 28: 158, 1953.
10. CONWAY, E. J. *J. Physiol.* 130: 427, 438, 1955.
11. AEBI, H. *Biochem. J.* 54: PROC. XI, 1953.

Intermediary metabolism

Editor's summary

R. W. BRAUER

Naval Radiological Defense Laboratory, San Francisco, California

THE STUDY OF CHANGES in intermediary metabolism during cold acclimation entails the search for phenomena with which to construct an integrated picture concerning the chemical nature of regulatory processes significant to the physiology of mammals in a cold environment. As is well documented in the preceding pages, this search for phenomena is bearing fruit at almost all levels of metabolic study; thus changes have now been reported in carbohydrate, fat and protein metabolism, in tissue enzyme complements, energy production rates, fluid and electrolyte distribution, hormonal balance and in growth rates.

However, the accruing data still present a rather chaotic appearance. One of the causes for this confused picture has been obvious in the course of the discussion of this session, viz. no two investigators have employed the same experimental conditions with respect to such factors as food quality, ambient temperatures, humidities and rates of air movement, ages and breeds of the test animals, condition of hair, type of cage, manner of animal handling, time and manner of sacrifice; all are different between any two investigations reported here. Since the essence of the changes accompanying acclimatization is the ability of the organisms under experiment to respond to their environment and to reflect in their biology their life history, it is little short of a miracle that any sort of agreement should have been attained among so diverse an array of studies.

Cold acclimation is the result of cold exposure. Of necessity, it entails a change in the subject's temperature gradient map. This is more likely to be different at the start of exposure than at the end: ambient air of 2°C

means something different to the adapted than it does to the nonadapted subject. Since the metabolism of cooled tissues is an integral part of the metabolic pattern of cold acclimation, one wonders whether one should not seek biochemical comparisons between similar histological assemblies near the surface and near the core; yet to date, such studies have at best been touched upon very lightly. In order to assess the meaning of any biochemical changes occurring in the course of cold adaptation, one should probably look at the actual temperatures under which the various tissues function *in vivo* and do one's testing at those temperatures, rather than at some arbitrary temperature level; even better perhaps, would be the testing of the effect of tissue temperature changes upon the several reaction chains. Again, all of our discussion has dealt with the small mammal in which thermogenesis overshadows all other aspects of cold adaptation. Of specific interest also are the metabolic aspects of the cooled appendages of certain larger mammals and birds of the Arctic regions.

Cold exposure sufficiently severe to lead to cold acclimation entails a gross shift in nutritional balance; the final product of the process of cold acclimation is not only a sadder and wiser, but also a leaner and perhaps a drier, animal than before. Yet when the rat in the process of adapting itself to a cold environment undergoes a drastic change in body composition, involving a marked shift in the proportions of different tissue elements making up the body, we all too often ignore this and pick out a 'representative' piece of tissue, analyze this, and draw conclusions from it. A well designed study of balance and composition would seem to promise very tangible returns in terms of classifying the role of these changes in the phenomenology of cold acclimation. Closely allied to this point of view are the questions of when is a control a control, and the nature and constitution of comparable stresses for experimental analysis of differences between adapted and nonadapted subjects.

Finally, one can turn to the question of which metabolic changes contribute the basis for the specific metabolic response of thermogenesis, i.e. the metabolic phase of cold acclimation. It appears that this phase of the subject throws into focus a basic problem of the biochemistry of homeostasis. The metabolic changes of cold acclimation might better be characterized as those that lead to a sustained increase of metabolic performance which remains in keeping with homeostasis of the entire organism, rather than depending upon the maximal metabolic capacity of certain systems. This over-all controlled pattern could well account for the limited changes found to occur in acclimation.

V

Cellular and Subcellular Energetics

Chairman: L. F. LELOIR

Factors which affect cold acclimatization[1]

A. KURT WEISS

Department of Physiology, University of Miami School of Medicine, Coral Gables, Florida

WEISS, A. KURT. *Factors which affect cold acclimatization.* Fed. Proc. 19, Suppl. 5: 137–138. 1960.—Acclimatization to cold is best achieved by the relatively young rat. The ability to achieve this acclimatization by metabolic means depends in part upon the availability of endocrine reserves. When these can be mustered they bring about an increase in heat production to balance the increased heat loss. In older or senescent rats where inadequate endocrine reserves prevent metabolic acclimatization to cold, the administration of thyroid compounds can bring about artificial acclimatization.

ALTHOUGH BOTH THE SHIVERING and metabolic activities of the neuromuscular system of cold-exposed animals have been the subject of much study for a number of years (1, 2), it was only in the early 1950's that You and Sellers successfully demonstrated that the oxygen consumption of liver slices of rats accustomed to living in a cold environment were higher than those of animals kept at room temperature (3). These findings suggested that there is an increase in the metabolic activity of visceral as well as of muscular tissues in the cold-exposed animal. Weiss has extended these findings and shown that in addition to the liver other visceral organs participate in the cold-induced alterations of the metabolic rate (4). By contrast, he has also demonstrated that the metabolic rate of a number of other tissues does not seem to be affected by cold exposure of the intact animal.

The increases in metabolic rate which have been mentioned represent adaptive changes, i.e. they increase the animals's resistance to the stressful situation, in this case cold exposure. In the final analysis they produce alterations in the heat-producing mechanism of the stressed rat whereby increased heat losses can be balanced out. In this manner the total heat losses equal the total heat production and near-normal thermal relationships can be maintained by the homeotherm. These changes which result from cold exposure thus represent actual alterations in the heat production machinery of the stressed animal and persist for a certain period of time even after the stressor has been removed.

[1] Supported in part by grants from the National Institutes of Health.

TISSUE RESPONSES

The liver, diaphragm, heart, extensor digitorum longus, kidney cortex and skin epidermis were found to increase their metabolic rate upon exposure to cold. The thymus, lung, testes, intestinal smooth muscle, cerebral cortex, spleen and dermis retain their pre-exposure levels of metabolic rate even after a severe and prolonged experience of cold exposure (4). An interesting fact is the similarity of the qualitative aspect of the responses obtained when tissue slices from cold-adapted animals are compared with those from animals treated with single or multiple doses of thyroid hormone. The available comparative data indicate that tissues showing elevated metabolic rates as a result of cold exposure will also show these responses to thyroid treatment of the intact animal; conversely, in tissues where cold exposure cannot bring about adaptive changes, the *in vivo* administration of thyroid compounds does not bring about alterations in the metabolic rate (5, 6). The evidence suggests that, in addition to other pathways and influences, the thyroid gland plays an important role in the regulation of the oxygen consumption levels of selected tissues and in the subsequent success of acclimatization.

AGE AND ACCLIMATIZATION

The processes which have been discussed so far have been observed in 6- to 16-week-old rats and very likely could also be noted in rats somewhat younger or older than this age spread. However, when weanling rats (about 4 weeks old) are exposed to cold it is often impossible to demonstrate adaptive changes (7). This is because, in our experience, either the animals succumb to the effects of the severely cold environment or, when

the severity of the cold stress is reduced, the animals can survive the sufficiently diminished intensity of cold long enough for more effective responses to develop.

As an animal grows older the ability to acclimatize at first improves, but eventually becomes progressively impaired. To cite specific cases: 6-week-old rats will acclimatize easily, but when 6-month-old Holtzman rats are exposed to 5°C for 10 days no changes in the tissue oxygen consumptions can be noted, with the exception of liver slices. Prolongation of the cold exposure experience does not alter this picture, nor does lowering the temperature at which the animals are exposed bring about adaptive changes in the other tissues (7).

From this evidence it can be concluded that it is indeed fortunate that the cold acclimatization processes of the rat were first studied with an age group which demonstrates the most extensive adaptive responses; for had the initial experiments been performed on a considerably older group of rats the erroneous conclusion might have been made that among the many tissues investigated the liver alone undergoes metabolic alterations.

It seems that there is still some lack of clarity on the subject of acclimatization to cold in the rat and therefore there is a need to summarize again what is known about this process: Many metabolic responses in acclimatization to cold occur only in the relatively young rat (analogous in age to school children of the human race); the processes are not fully developed in very young rats, and seem to decline in the older animal. This is a point which has frequently been overlooked in the literature on this subject. It should be noted that the emphasis is upon metabolic responses and it is not suggested that nonmetabolic processes become altered in the same manner.

ARTIFICIAL ACCLIMATIZATION

Is there any way in which older or senescent rats can be made to acclimatize to cold by artificial means? Sellers and co-workers investigated the problem of artificial acclimatization to cold some years ago (8). By pretreating clipped, nonacclimatized rats with endocrine and other compounds, singly and in combination with each other, they succeeded in increasing the survival rate in cold. This work was done on Wistar rats averaging 200 grams in weight.

Will similar pretreatment also increase the survival rate of older rats? This question was answered when Holtzman rats between the ages of 6 months and 2 years were exposed to 5°C for at least 1 week. Although these animals were able to live in the cold, the tissues did not demonstrate increased oxygen consumption rates (9). When these pre-exposed animals were clipped and continued to be exposed to the cold they soon died. Artificial acclimatization could be brought about, however, by injection of large doses of thyroid compounds. In our laboratory triiodothyronine acetate was administered on 3 alternate days during pretreatment with cold. Maintenance doses of this compound continued to be supplied after the animals were clipped. The treated animals continued to be clipped twice a week. Although the older animals required larger doses, it was possible to maintain them in the cold for as long as 2 weeks after the initial clipping by carefully adjusting the dosage to the needs of each individual rat. The dosages were of a magnitude that would bring about thyrotoxicosis in normal animals, but under these experimental conditions they made survival possible, at least within the limits of the experiment. It is quite likely that artificial acclimatization can be induced in even older rats.

CONCLUSION

These results suggest that the ability of the rat to achieve adaptation to cold by metabolic means which will allow the organism to successfully withstand the effects of cold depends in part upon the availability of endocrine reserves. Where these can be mustered they bring about an increase in the heat production which balances the increased heat loss. Where such reserves are not available therapeutic means can be employed to bring about artificial acclimatization.

Triiodothyronine acetate was kindly supplied by Mr. John F. Buckley of Smith, Kline & French Laboratories, Philadelphia.

REFERENCES

1. Burton, A. C. and D. W. Bronk. *Am. J. Physiol.* 119: 284, 1937.
2. Hemingway, A. and S. R. Hathaway. *Am. J. Physiol.* 134: 596, 1941.
3. You, R. W. and E. A. Sellers. *Endocrinology* 49: 374, 1951.
4. Weiss, A. K. *Am. J. Physiol.* 188: 430, 1957.
5. Barker, S. B. *Proc. Soc. Exper. Biol. & Med.* 90: 109, 1955.
6. Whaley, R. A., T. M. Hart and H. M. Klitgaard. *Am. J. Physiol.* 196: 1258, 1959.
7. Weiss, A. K. *Am. J. Physiol.* 177: 201, 1954.
8. Sellers, E. A., S. Reichman and E. Thomas. *Am. J. Physiol.* 167: 644, 1951.
9. Weiss, A. K. *Fed. Proc.* 18: 168, 1959.

Tissue energy metabolism in the cold-acclimatized rat

JOHN P. HANNON
Physiology Department, Arctic Aeromedical Laboratory, APO 731, Seattle, Washington

HANNON, JOHN P. *Tissue energy metabolism in the cold-acclimatized rat.* Fed. Proc., Suppl. 5: 139–144. 1960.—Data are given relating the effect of duration of cold exposure on liver slice and whole-body oxygen consumption of laboratory rats. Data are also presented on the effect of cold exposure on various liver oxidase activities, oxidative phosphorylation and adenosine triphosphatase activities. The comparative study of electron transport components in liver and muscle is given. These data are discussed in relation to the development of nonshivering thermogenesis and the cellular metabolic control mechanisms in the cold-acclimatized animals.

IN THIS SYMPOSIUM, we have heard many references to alterations in the oxidative metabolism of the intact, cold-acclimatized animal. And we have heard from Dr. Smith, Dr. Weiss and Dr. Masoro, as well as myself in an earlier session, a somewhat limited discussion of the cold-induced alterations in tissue metabolism. At this time, I would like to bring out certain aspects of cellular energy metabolism that as yet have not been considered.

First, we might legitimately ask the question: Is there any correlation between 'whole-body metabolism' and the *in vitro* tissue metabolism of the cold-acclimatized rat? Affirming this, figure 1 gives data taken from Cottle and Carlson (1) showing the oxygen consumption of the intact rat, measured at 5°C, plotted with some of my own data (2) showing the endogenous oxygen consumption of liver slices as well as the oxygen consumption of slices incubated in Krebs-Henseleit Ringer solution in the presence of lactate and β-hydroxybutyrate. Besides indicating a striking similarity between the response of the intact animal and the response of the liver to cold exposure, these data bring out three other factors of interest. The first of these is that the length of exposure to cold influences the metabolic response. Thus, in both the intact animal and in liver tissue, we observe a rising and a declining phase of oxygen consumption as the exposure interval is lengthened. We observe also that the relative magnitude of these changes when plotted as a function of time is quite similar for the two types of measurements. The changing nature of the metabolic response, however, brings up the controversial question of at what stage of cold exposure do we consider the animal acclimatized. Is it at 3–5 weeks, when he has reached his maximum metabolic response, or is it at intervals of exposure longer than 2 months, when metabolic rates have returned toward control levels?

The second factor concerns the mechanisms responsible for the initially rising and later declining response of the intact animal, as well as his liver tissue, to cold. The initial rise is perhaps somewhat easier to explain. Thus, we have good evidence in the intact animal that it is the result of an increased activity of the thyroid and possibly the adrenal medulla (3). Similarly, we have heard from Dr. Smith and have reports in the literature (4–6) that an augmented thyroid activity may explain the changes observed at the tissue level. This will be considered in more detail later. About the declining phase of whole-body and liver metabolism, we know virtually nothing, and it is this aspect of cold exposure that needs much more work at both the tissue and the whole animal levels, if only to clarify the current discrepancies in the literature.

The third factor concerns the nature of the substrates and the enzyme mechanisms responsible for the augmented metabolism in both the intact animal and its tissues. As seen in figure 1, the data on liver tissue are, in the main, a reflection of the oxidation of endogenous substrate, since the values obtained in the absence of added substrate are not much lower than those obtained in the presence of lactate or β-hydroxybutyrate. Little is known either of the endogenous constituents being metabolized or of the enzyme changes possibly involved.

It should be emphasized also that increases similar to those in liver have been observed in muscle, kidney, heart (7–9) and skin (10). On the other hand, Weiss (8) reported that in rats exposed for 5 days at 5°C thymus, testis, brain, spleen, intestinal smooth muscle, lung and in some instances kidney tissue did not show an increased Q_{O_2}. Whether or not these latter tissues would have shown an increased respiration following longer exposures is not known, but it is significant that those tissues comprising a large portion of the 'metabolizing mass' of the animal do show the response.

Concerning the metabolites supporting the elevated metabolism of liver and other tissues, very little is known directly. Indirectly, the blood of the 1-month ac-

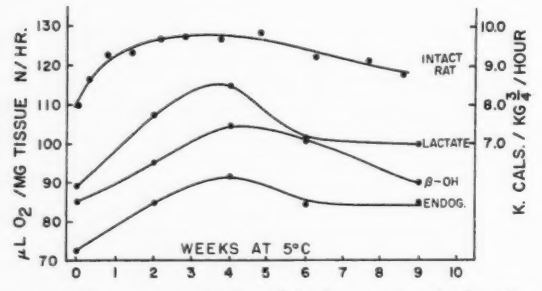


FIG. 1. Oxygen consumption of the intact rat and of rat liver tissue as a function of time of exposure to cold.

climatized animal has been observed (11) to have elevated levels of nonprotein nitrogen which in part consist of amino acids (unpublished observations) and higher levels of phospholipid, cholesterol and ketone bodies. The levels of sugar and neutral fats were unaltered by cold exposure, although an increased turnover of blood sugar was indicated by the fact that blood levels were maintained just as well in the fasted, cold-acclimatized animal as in their fasted controls. Studies (12–17) on urine chemistry of the cold-acclimatized rat give a somewhat similar picture to that observed in blood, i.e. an increased excretion of nitrogenous compounds. Aside from glycogen determinations, relatively few direct measurements of tissue metabolite levels have been made in cold-acclimatized rats, and in this area much more work needs to be done. Data on the gross chemistry of the liver of the 1-month acclimatized rat indicate that the only substantial major effect of the exposure is to elevate phospholipid and cholesterol levels (11), which suggests that lipid is being metabolized at augmented rates. Page (18), Hart and Heroux (19) and Mefford, Nyman and Hale (20) among others, arrived at similar conclusions.

In order to gain some idea of the effect of prolonged cold on enzyme systems, we decided to get away from the use of slice preparations and to use some other form of tissue preparation where endogenous rates were not so high. From this standpoint alone, mitochondrial preparations would have been the ones to choose, but there are two serious drawbacks to their use when one is attempting to relate their activities to that of the whole organ. One of these was excellently demonstrated by Dr. Smith, when he showed that different degrees of washing of mitochondrial preparations led to entirely different results. Thus, it is possible to 'wash out' certain metabolic effects of cold exposure in making up the tissue preparation. An even more serious objection would be an unequal 'washing out' between the control and cold-exposed mitochondrial preparations. Such a possibility is suggested by the data of Panagos, Beyer and Masoro (4) where a differential mitochondrial swelling rate between cold-exposed and control animals is indicated. A second objection to the use of mitochondrial preparations for studying enzymes and enzyme systems and relating the results to the whole organ or the whole animal was the uncertainty as to the degree of recovery from the whole homogenate.

Thus for the present studies on the effect of cold exposure on enzymes and enzyme systems we chose the whole homogenate. The first of such studies was conducted on rats that had been cold-acclimatized for 1 month, i.e. that exposure giving the maximum oxidative rate in liver slices. Again liver tissue was used, the preparation consisting of a 10% sucrose homogenate containing ethylenediaminetetraacetic acid (pH 7.4), and the oxidation of a variety of substrates was examined (table 1).

Although not as markedly as in the slice experiments, the endogenous respiration of the homogenates was elevated following cold acclimatization, as was the oxidation of a large number of intermediates including those of the Krebs' cycle. In fact, the only exception was lactate oxidation, in which no cold effect was evident.

The data obtained with liver homogenates permit three general conclusions concerning oxidative metabolism of liver in the cold-acclimatized animal. First, the higher than normal oxidative metabolism can be supported by a variety of substrates, including degradation products of protein and lipid. Second, since the substrates are used at their optimal concentrations, the measured rates are indicative of an increase in oxidative enzyme activity. Third, since all of the substrate oxidations that proceed at elevated rates are catalyzed by enzymes located in the mitochondria, it can be concluded that cold exposure has brought about some alteration in these subcellular structures. Per unit weight of tissue, this alteration could involve an increase in mitochondrial number, an increase in mitochondrial size with a concomitant increase in the amount of enzyme, a physical or chemical alteration of the mitochondrial structure so as to release latent enzyme activity, or any combination of these three variables.

TABLE 1. *Effect of 4 Weeks Cold Exposure on Oxidation of Various Substrates by Rat Liver Homogenates*

Added Substrate	Control			Cold-Exposed			% Change	P
	N	Mean	S.E.	N	Mean	S.E.		
None	15	53.6	±1.40	12	58.1	±1.53	+8.4	<0.05
Lactate	8	20.0	±0.70	7	20.9	±1.68	+4.5	n.s.
Glutamate	15	153.1	±3.52	11	184.0	±5.90	+20.8	<0.01
β-Hydroxybutyrate	15	130.0	±3.80	9	173.3	±4.31	+33.0	<0.01
Citrate	15	142.1	±3.73	12	169.7	±3.69	+19.4	<0.01
Isocitrate	7	100.9	±6.90	6	135.1	±8.09	+33.9	<0.01
α-Ketoglutarate	15	145.3	±4.06	9	187.0	±5.09	+28.7	<0.01
Succinate	8	208.2	±9.33	6	285.1	±8.70	+37.2	<0.01
Fumarate	12	94.6	±3.85	13	111.8	±2.42	+18.2	<0.01
Malate	4	96.6	±1.14	6	115.8	±1.53	+19.9	<0.01

Oxidative rates are expressed in µl of O_2 consumed per mg of tissue N per hr. All rates except endogenous, which is labeled *None*, are corrected for endogenous O_2 consumption. From Hannon (22).

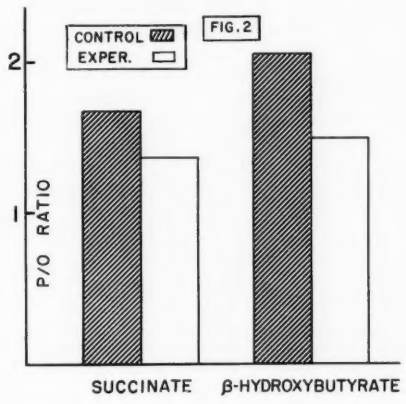
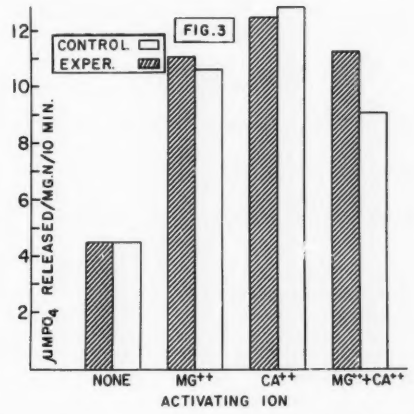


FIG. 2. Oxidative phosphorylation. Effect of 4 weeks cold exposure on P/O ratios for β-hydroxybutyrate and succinate oxidation by rat liver homogenates.

FIG. 3. Effect of 4 weeks cold exposure on the ATPase activity of water homogenates of rat liver tissue. Calcium and magnesium, where used, were each added to a final concentration of 0.005 M.



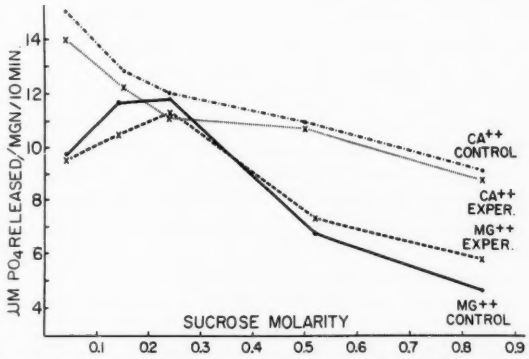


FIG. 4. Effect of 4 weeks cold exposure on the ATPase of rat liver tissue when measured at various sucrose medium tonicities. Calcium and magnesium were added to a final concentration of 0.005 M.

One mechanism whereby oxidative rates could be elevated is through an uncoupling of oxidative phosphorylation. Accordingly, since it is well established (21) that the rate of oxidase activity is proportional to the availability of adenosinediphosphate, any condition that makes more ADP available tends to increase the rate of oxygen consumption. An uncoupling of oxidative phosphorylation, i.e. a disassociation of the coupling between oxidative energy release and adenosinetriphosphate synthesis from ADP, would be just such a condition. That this condition indeed exists in the cold-acclimatized animal is witnessed by the reports of Panagos, Beyer and Masoro (4) and Smith and Fairhurst (5), using liver mitochondria, and more recently (fig. 2) at our laboratory with liver homogenates (6). It should be noted that an uncoupling such as that observed here could still allow a normal rate of ATP synthesis for the vital processes of the cell and at the same time allow more oxidative energy to be released directly as heat, an important factor to the cold-exposed animal.

The mechanisms behind the uncoupling of oxidative phosphorylation in the cold-exposed animal have, of course, been the object of considerable study and speculation (4–6); however, as these are adequately summarized elsewhere in the present Symposium they will not be further reviewed here.

Another mechanism whereby ADP could be made available at above-normal rates would be through an increase in adenosinetriphosphatase (ATPase) activity. ATPase, which includes a number of poorly defined enzymes, mediates the dephosphorylation of ATP to form ADP. Two experiments to determine whether cold exposure could lead to changes in the activity of ATPase are illustrated in figures 3 and 4. In figure 3, the activity was tested in water homogenates in the presence of calcium and magnesium as activating ions. Very little effect of cold exposure was observed in these experiments. In fact, the only instance in which a statistically significant difference was found to occur was that where both calcium and magnesium were present; in this case, there was a more pronounced depression in the cold-exposed group than in the control. In this experiment, therefore, we can find no indication that ATPase is acting to produce ADP at augmented rates in the liver of the cold-exposed animal.

Since water homogenization is known to cause mitochondrial swelling and thus give near-maximal ATPase activity in these structures, the possibility was considered that the tonicity of the medium in the foregoing experiment might have masked any difference that existed between the control and the cold-exposed groups. To test this possibility additional assays were conducted in sucrose homogenates. Here, both calcium and magnesium were used separately as activating ions, and a wide range of sucrose concentrations was used to regulate swelling. Again, little if any 'cold effect' was observable. On the basis of evidence so far accumulated, therefore, it seems very unlikely that oxidative metabolism is stimulated by high adenosinetriphosphatase activities in the cold-acclimatized rat liver.

In the experiments described thus far, we have not been able to decide whether the elevated activity on the part of various oxidases has been due entirely to an uncoupling of oxidative phosphorylation or due in part to

TABLE 2. *Effect of 4 Weeks Cold Exposure on the Succinoxidase System of Liver and Muscle*

Component	Control			Cold-Exposed			% Change	t
	N	Mean	S.E.	N	Mean	S.E.		
			Liver					
Succ. dehyd. complex	6	107.9	± 1.65	6	127.7	± 3.24	+16.8	5.44*
Succ. dehydrogenase	6	86.3	± 3.53	5	104.9	± 2.17	+21.5	4.48*
Cytochrome oxidase	6	535	±25.4	6	629	±22.2	+17.5	2.78*
			Muscle					
Succ. dehyd. complex	6	23.5	± 0.85	5	34.2	± 2.00	+49.7	4.91*
Succ. dehydrogenase	7	35.4	± 1.28	7	46.5	± 1.93	+31.4	4.78*
Cytochrome oxidase	6	68.8	± 4.93	7	91.0	± 5.12	+32.2	3.12*

Activities are expressed as μl O_2 consumed per gm of tissue per min. Incubation temperature 30°C. * Significant at the 0.05 level or better.

an increased oxidase enzyme activity per se. Furthermore, if there is an increase in oxidase activity not explainable by the uncoupling phenomenon, we do not know whether it is attributable to an activation of latent enzyme activity or to a true increase in enzyme concentration.

One approach to these questions lies in the determination of the specific activities of individual enzymes. This was done in several experiments in which the specific activities of various components of the electron transport system in liver and muscle tissue were investigated.

The first components of the electron transport system to be investigated were those involved in the oxidation of succinate, or more accurately, in the transfer of the hydrogen to oxygen following the conversion of succinate to fumarate (table 2). In both liver and muscle, cold exposure induced a significant increase in the activity of the succinic dehydrogenase complex; that is, in the complete sequence of electron transport components from the substrate, succinate, through the dehydrogenase to cytochrome *b*, and thence to cytochromes c_1 and *c*. This effect of cold is in agreement with earlier findings from this laboratory (22) and others (10, 23–25) where prolonged cold exposure was observed to increase activities of succinoxidase and succinic dehydrogenase complex in liver and skin. The increased activity in muscle is quite in contrast to that reported by Des Marais (25).

Since the succinic dehydrogenase complex is much less active than cytochrome oxidase, the complex constitutes the rate-limiting portion of the complete system. It was questioned, therefore, whether the increased succinoxidase activity of the cold-acclimatized animals was restricted to certain components of the dehydrogenase complex or involved cytochrome oxidase as well. To answer this question, specific assays were made on the dehydrogenase, which has a low activity rate, and on cytochrome oxidase, which has a high activity rate. In liver and muscle tissue, both of these enzymes exhibited increased activity following prolonged cold exposure; hence, the effect of cold appeared to be general rather than specific.

A final and interesting result seen in these data was the more pronounced effect of cold acclimatization on the enzyme activities of muscle tissue than upon those of liver. In liver and muscle, respectively, the cold induced an increase of about 18% and 45% in the activity of succinic dehydrogenase complex, in succinic dehydrogenase about 21% and 31% and in cytochrome oxidase about 17.5% and 33%. Thus, cold acclimatization resulted in an increase in enzyme activity of muscle over that of liver ranging from about 50% for succinic dehydrogenase to about 250% in the case of succinic dehydrogenase complex. To avoid confusion, it should be observed that the absolute level of all these components is much higher in liver than in muscle.

The second system of hydrogen transport between substrates and oxygen to be investigated was that linked to diphosphopyridine nucleotide (DPN). The terminal stages, i.e. from cytochrome *c* to oxygen, are the same in this system as in succinoxidase. However, the initial stages are represented by at least two different components. The first of these, DPN, serves as a coenzyme to various dehydrogenases, and the second, DPNH-cytochrome *c* reductase, links the coenzyme to cytochrome *c*. To study the effect of cold acclimatization on the activity of this system in liver and muscle, two different dehydrogenases were selected for assay: the first, lactic dehydrogenase, was chosen to represent a dehydrogenase that existed in the soluble portion of the cytoplasm whereas the second, malic dehydrogenase, was chosen to represent a dehydrogenase that existed in the particulate (mitochondrial) portion of the cytoplasm. DPNH-cytochrome *c* reductase is found generally distributed in the microsomal and mitochondrial fractions.

It was observed (table 3) that cold exposure had a differential effect on this sytem in both liver and muscle tissue. Thus, the activity of the lactic dehydrogenase was unaffected in either liver or muscle by cold exposure. Malic dehydrogenase, on the other hand, exhibited an increased activity in both tissues following cold exposure. Finally, DPNH-cytochrome *c* reductase activity of these tissues was unaffected by the cold exposure.

The absence of a cold effect in lactic dehydrogenase and the stimulatory effect in malic dehydrogenase are in agreement with data in table 1 on the complete lactic and

TABLE 3. *Effect of 4 Weeks Cold Exposure on Activities of DPNH-Linked Enzymes of Liver and Muscle Tissue*

Enzyme	Control			Cold-Exposed			% Change	t
	N	Mean	S.E.	N	Mean	S.E.		
Liver								
Lactic dehydrogenase	8	827	±19.8	8	792	±21.6	−4.2	1.19
Malic dehydrogenase	4	726	±13.0	4	862	±9.3	+18.7	8.53*
DPNH-cyto *c*. reductase	3	33.2	±0.73	3	34.9	±0.81	+5.1	1.56
Muscle								
Lactic dehydrogenase	8	1123	±29.7	8	1093	±16.4	−2.6	0.88
Malic dehydrogenase	5	785	±36.2	5	1003	±32.9	+27.8	4.45*
DPNH-cyto *c*. reductase	3	1.40	±0.055	3	1.25	±0.066	−10.7	0.93

Activities are expressed as ΔO.D. per min. per gm of tissue at 340 mμ for lactic and malic dehydrogenases and at 550 mμ for DPNH-cytochrome *c* reductase. * Significant at the 0.05 level or better.

TABLE 4. *Effect of Metabolic Stimulators of Liver Succinic and Malic Dehydrogenase Activities of Control and Cold-Exposed Rats*

Addition	Succinic Dehydrogenase				Malic Dehydrogenase			
	Control	Cold-exp.	Δ	Aver.*	Control	Cold-exp.	Δ	Aver.*
None	82.2	104.6	22.4	93.4	628	764	136	696
Thyroxin	89.9	110.9	21.0	100.4	690	790	100	740
Dinitrophenol	89.1	108.8	19.7	99.0	729	857	128	793
Hexo.-gluc.	99.2	116.2	17.0	107.7				
PO_4	90.6	112.6	23.0	101.6				
Hexo.-gluc.-PO_4	93.8	114.5	20.7	104.2				

Activities are expressed as μl of O_2 consumed per gm of tissue per min. for succinoxidase, and as Δ $O.D._{340}$ per gm of tissue per min. for malic dehydrogenase. * Critical differences ($P \leq 0.05$) between averages are: succinic dehydrogenase, 3.70; malic dehydrogenase, 19.7.

malic oxidase systems of liver tissue from cold-exposed animals. Results similar to these for DPNH-cytochrome *c* reductase have been reported by Smith (*loc. cit.*) and for TPNH-cytochrome *c* reductase in liver mitochondria by Smith and Fairhurst (5).

Three additional points to be noted in these data are: first, the more pronounced effect of cold on muscle tissue compared with liver tissue in the case of malic dehydrogenase (an increase about 50% greater); second, the similarity in the general level of liver and muscle activities for lactic and malic dehydrogenases (in contrast to succinic dehydrogenase where the muscle activity is considerably lower than that of liver); and third, the extremely low DPNH-cytochrome *c* reductase activity in muscle compared with liver.

With the exception of lactic dehydrogenase, all the electron transport components studied here are partly or wholly associated with mitochondrial structure. Because of this and the fact that a large number of mitochondrial enzyme activities have been shown to be influenced by structural changes, experiments were undertaken to determine whether the cold-induced increases in enzyme activity could be attributed to changes in mitochondrial structure, i.e. through an activation of latent enzyme activity. As test enzymes, the succinic and malic dehydrogenase activities of liver tissue from control and cold-exposed animals were used. Thyroxin (1 μg/ml), 2,4-dinitrophenol (1×10^{-5} M), hexokinase-glucose (0.155%, 0.033 M), phosphate (0.05 M), and phosphate-hexokinase-glucose (0.05 M, 0.166%, 0.033 M) were respectively included in the basic assay media to bring about mitochondrial swelling. The data from these experiments are presented in table 4.

Grossly, it can be readily observed that each of these agents, where used, stimulates both succinic and malic dehydrogenase activity. Besides this general effect, three other points are pertinent. First, the magnitude of the increase wrought by each of these agents was essentially the same in the cold-exposed group as in the control group. In other words, the differential between the means of the cold-exposed and control groups was maintained. Second, the magnitude of the increase in activity brought about by these agents was significantly different in several cases. This can be inferred from the averages shown in table 4. Briefly, in the succinic dehydrogenase data, there were similar degrees of response to thyroxin, 2,4-dinitrophenol and phosphate and a significantly more pronounced response to hexokinase-glucose. Furthermore, there was no summation of the hexokinase-glucose and the phosphate stimulations. In the malic dehydrogenase data, the stimulation of the activity by 2,4-dinitrophenol was significantly greater than that by thyroxin.

Now to attempt to answer a question posed earlier: Is the increased tissue oxidative activity due to an uncoupling of oxidative phosphorylation, an activation of latent enzyme activity, or to an absolute increase in enzyme concentration? The data on succinic and malic dehydrogenase, as well as that on cytochrome oxidase, answers the first part of the question by indicating that the uncoupling of oxidative phosphorylation is not the sole means whereby tissue oxidative activity is increased. This conclusion is based on the fact that these enzymes were assayed under conditions where no phosphate esterification was occurring.

A decision on whether the augmented activity is due

to an activation of latent activity or to an absolute increase in enzyme concentration is somewhat more difficult. Obviously, since cold exposure produced no alteration in lactic dehydrogenase and DPNH-cytochrome *c* reductase, neither possibility need be considered in their cases. Support for the stimulation of latent activity is found in the data in table 4 where it was shown that certain natural (thyroxin, hexokinase-glucose, and inorganic phosphate) and unnatural (2,4-dinitrophenol) substances are capable of increasing the activity of succinic and malic dehydrogenases, probably by way of their swelling effect on mitochondria (26). On the other hand, since these substances produced almost equal increases in the activities of the enzymes from the control and the cold-acclimatized animals, and since no summation of the effects of these substances could be demonstrated, a strong case for an absolute increase in enzyme concentration is presented. If an activation of latent activity had been the only mechanism, besides the uncoupling of oxidative phosphorylation, we would have expected a differential effect of these substances; that is, they would have raised the activities of the dehydrogenase towards the same level of activity in the cold and control groups.

In conclusion then, data accumulated to date seem to indicate that in achieving higher rates of oxidative metabolism the cold-acclimatized rat makes use of three basic mechanisms, acting at the enzyme level. These are: *1*) an uncoupling of oxidative phosphorylation; *2*) an activation of latent enzyme activity; and *3*) an absolute increase in the concentrations of certain, probably rate-limiting, oxidative enzymes, e.g. dehydrogenases.

We might even speculate with some confidence on the agents responsible for the enzyme changes that we have observed. Thus, it is well recognized that thyroid hormone plays an important role in the oxidative metabolism of the cold-exposed animal (27–31). In addition to the indirect effects on oxidations produced through mitochondrial swelling (26), there now is evidence (4–6) that this hormone probably acts to uncouple oxidative phosphorylation in the cold-acclimatized animal. This would, in effect, amount to releasing the 'brake' imposed on the oxidative processes by a nonavailability of adenosinediphosphate for the coupled synthesis of adenosinetriphosphate (21).

There is also a distinct possibility that hexokinase may may be acting directly to influence the activity level in liver and muscle. Pertinent to the present experiments, it was reported in an earlier session that cold-acclimatized animals exhibit approximately 30 % higher liver hexokinase and approximately 50 % higher muscle hexokinase than do control animals. This is even more significant when one considers the fact that a sizable portion of hexokinase has been reported (32, 33) to reside in the mitochondria—thus giving a physical association of oxidative enzymes and hexokinase within the cell. Consequently, if hexokinase does act directly, as the experiments on succinic and malic dehydrogenase would indicate, a high tissue level of hexokinase could lead to augmented oxidative rates. Finally, we should not overlook the fact that the rate and direction of movement of a substrate over its particular enzyme system is governed by mass law considerations as well as by the level of the enzyme activity. It is in this area of reactant (substrate) and product concentrations within the cells of the cold-acclimatized animal that our current information on intermediary metabolism is most deficient.

REFERENCES

1. Cottle, W. and L. D. Carlson. *Am. J. Physiol.* 178: 305, 1954.
2. Hannon, J. P. *Am. J. Physiol.* 192: 253, 1958.
3. Swanson, H. E. *E ndocrinology* 60: 205, 1957.
4. Panagos, S., R. E. Beyer and E. J. Masoro. *Biochem. et biophys. acta* 29: 204, 1958.
5. Smith, R. E. and A. S. Fairhurst. *Proc. Natl. Acad. Sci. U. S.* 44: 705, 1958.
6. Hannon, J. P. *Am. J. Physiol.* 196: 890, 1959.
7. Weiss, A. K. *Am. J. Physiol.* 177: 201, 1954.
8. Weiss, A. K. *Am. J. Physiol.* 188: 430, 1957.
9. Weiss, A. K. and W. G. Moss. *J. Applied Physiol.* 10: 131, 1957.
10. Des Marais, A. *Canad. J. Biochem. & Physiol.* 33: 758, 1955.
11. Hannon, J. P. and D. W. Young. *Am. J. Physiol.* 197: 1008, 1959.
12. You, S. S., R. W. You and E. A. Sellers. *Endocrinology.* 47: 156, 1950.
13. Young, D. R. and S. F. Cook. *Proc. Soc. Exper. Biol. & Med.* 89: 482, 1955.
14. Bodansky, M. and V. B. Duff. *Endocrinology.* 20: 822, 1936.
15. Chinn, H. I., F. W. Oberst, B. Nyman and K. Fenton. Proj. No. 21-23-027, SAM, Randolph Field, Texas, 1950.
16. Mefferd, R. B., Jr. and H. B. Hale. *Am. J. Physiol.* 195: 726, 1958.
17. Mefferd, R. B., Jr., H. B. Hale and H. H. Martens. *Am. J. Physiol.* 192: 209, 1958.
18. Page, E. *Rev. Can. Biol.* 16: 269, 1957.
19. Hart, J. S. and O. Heroux. *Canad. J. Biochem & Physiol.* 34: 414, 1956.
20. Mefferd, R. B., M. A. Nyman and H. B. Hale. SAM Tech Rep. 58–116, 1958.
21. Chance, B. In *Enzymes: Unit: of Biological Structure and Function,* edited by O. H. Gaebler. New York: Acad. Press, 1956, p. 447.
22. Hannon, J. P. *Proc. Soc. Exper. Biol. & Med.* 97: 368, 1958.
23. Clark, R. T., H. I. Chinn, J. A. Ellis, N. E. R. Pawel and D. Criscuolo. *Am. J. Physiol.* 177: 207, 1954.
24. You, R. W. and E. A. Sellers. *Endocrinology* 49: 374, 1951.
25. Des Marais, A. *Rev. Can. Biol.* 13: 115, 1954.
26. Lehninger, A. L. In *Enzymes: Units of Biological Structure and Function,* edited by O. H. Gaebler. New York: Acad. Press, 1956, p. 217.
27. Leblond, C. P. and J. Gross. *Endocrinology* 33: 155, 1943.
28. Sellers, E. A. and S. S. You. *Am. J. Physiol.* 163: 81, 1950.
29. Dempsey, E. W. and E. B. Astwood. *Endocrinology* 32: 509, 1943.
30. Woods, R. and L. D. Carlson. *Endocrinology* 59: 323, 1956.
31. Cottle, M. and L. D. Carlson. *Endocrinology* 59: 1, 1956.
32. Crane, R. K. and A. Sols. *J. Biol. Chem.* 203: 273, 1953.
33. Jervall, K. F., W. Walaas and O. Walaas. *Acta physiol. scandinav.* 35: 321, 1956.

Comments on oxidative phosphorylation in relation to cold acclimation

ROBERT E. BEYER[1]
Department of Physiology, Tufts University School of Medicine, Boston, Massachusetts

As one recently involved in the study of possible mechanisms of increased thermogenesis during cold acclimation (1–3), I would like to present some general thoughts on the subject. Shivering during the initial phase of response to cold leads to thermogenesis by three possible mechanisms: *a*) one deriving from implications of the *in vitro* experimental work by Abood *et al.* (4), in which electrical stimulation of mitochondrial suspensions produced abrupt and significant changes in the phosphorylative ability of these cytoplasmic particles to synthesize ATP; *b*) a possibility that the adrenal medullary hormone affects the efficiency of ATP synthesis (Lianides and Beyer, unpublished observations); *c*) the regulatory role of ADP in oxidative phosphorylation demonstrated recently in intact mammalian cells by Chance and Hess (5) which allows for an increased oxygen consumption and ATP synthesis in a tightly coupled system.

It is known that after several days of cold exposure the laboratory rat enters a phase of increased metabolic activity in which heat through shivering declines and that from 'chemical' thermogenesis appears. Two questions arise: first, about the mechanism allowing for this increased heat production and second, about the nature of the mediator responsible for regulating such a mechanism. Potter (6) has suggested that during cold acclimation substrate oxidation increases by way of the reduced triphosphopyridine nucleotide (TPNH)-cytochrome *c* reductase pathway. Preferential use of this poorly phosphorylating system would result in the formation of one ATP molecule in the passage of a pair of electrons from substrate to oxygen (7). However, evidence so far obtained shows no significant alteration in the enzyme activities mediating the TPNH-cytochrome *c* reductase pathway during cold acclimation (8, 9). A second pathway for additional heat production might be one entailing a loosening of the control which phosphorylation ordinarily exerts on the rate of electron transport, as suggested by Hoch and Lipmann (10) to apply in systems from mildly thyrotoxic rats. Thus a 'loose' coupling of respiration to phosphorylation could result in a lowering of the P/O ratio which is experimentally observed in cold-acclimated animals (1, 2, 8, 9). Since the animal acclimating to cold appears to raise its thyroid output (11–14), it would appear reasonable to propose the thyroid hormone as the mediator of the mechanism for increased heat production in chronic cold acclimation.

[1] Senior Research Fellow, U.S. Public Health Service.

REFERENCES

1. Panagos, S. and R. E. Beyer. *Fed. Proc.* 17: 121, 1958.
2. Panagos, S., R. E. Beyer and E. J. Masoro. *Biochim. et biophys. acta* 29: 204, 1958.
3. Lianides, S. P. and R. E. Beyer. *Fed. Proc.* 18: 92, 1959.
4. Abood, L. G., R. W. Gerard and S. Ochs. *Am. J. Physiol.* 171: 134, 1952.
5. Chance, B. and B. Hess. *J. Biol. Chem.* 234: 2404, 1959.
6. Potter, V. R. *Fed. Proc.* 17: 1060, 1958.
7. Vignais, P. V. and P. M. Vignais. *J. Biol. Chem.* 229: 265, 1957.
8. Smith, R. E. *Fed. Proc.* 17: 1069, 1958.
9. Smith, R. E. and A. S. Fairhurst. *Proc. Natl. Acad. Sci. U.S.* 44: 705, 1958.
10. Hoch, F. L. and F. Lipman. *Proc. Natl. Acad. Sci. U.S.* 40: 909, 1954.
11. Cottle, M. and L. D. Carlson. *Endocrinolology* 59: 1, 1956.
12. Leblond, C. P., S. Gross, W. Peacock and R. D. Evans. *Am. J. Physiol.* 140: 671, 1944.
13. Brown-Grant, K. J. *J. Physiol.* 131: 52, 1956.
14. Woods, R. and L. D. Carlson. *Endocrinology* 59: 323, 1956.

Mitochondrial control of oxidative phosphorylation in cold-acclimated rats[1]

ROBERT E. SMITH
Department of Physiology, University of California School of Medicine, Los Angeles, California

SMITH, ROBERT E. *Mitochondrial control of oxidative phosphorylation in cold-acclimated rats.* Fed. Proc. 19. Suppl. 5: 146–151. 1960. —The depression of oxidative phosphorylation observed in mitochondrial preparations from livers of either cold-acclimated or thyroxin-treated rats has been shown to depend upon the presence of extramitochondrial factors which are removed on further washing. These factors are demonstrable in the pink fluffy layer, where they are largely insensitive to the addition of bovine serum albumen (BSA) and their depressive effects on phosphorylation apparently unrelated to ATPase and glucose-6 phosphatase activities. Sonic oscillation of the fluff, or a crude lipid derived by cold ether extraction, both yielded factors which, though strongly inhibitory of phosphorylation, also become more sensitive to reversal by BSA and show degradative effects on phosphorylation which are due at least partly to ATPase activation. Of the six groups of fatty acids derived from the fluff lipid, the amount of the monoglycerides appeared lower in the cold than in the normal animals and the sterol esters and triglycerides higher. The latter like the mono- and diglycerides showed a higher specific activity in depressing P/O than when from control animals, but all effects were highly correlated with ATPase activity and largely reversible by BSA.

SURVIVAL OF THE LABORATORY RAT at reduced environmental temperature is achieved primarily by an increase of metabolic heat production sufficient to maintain normal body temperature.

In chronic exposure the initial emergency measures become gradually replaced by systemic and metabolic changes which are characterized in the term 'nonshivering thermogenesis.'

It was initially postulated (1, 2) that at this stage the tissue cells could be achieving this thermogenesis, not only by augmentation and alteration of total substrate utilization, but also by reduction of the proportion of energy immediately passed into the labile potential energy pool with relatively more energy being diverted directly into heat. This implies that, mechanically speaking, a lowering of net efficiency would be accepted as the price for a more effective system of heat production, to which might well attach a significant survival value during chronic cold exposure.

As applied to liver *in vitro*, this concept has achieved some support in the demonstration that the total oxygen cost of phosphorylation as measured by each of several methods is significantly raised in certain cell particulate fractions (1–3) and in liver homogenate (4) from cold-acclimated rats.

Whether this phenomenon enjoys a significant role *in vivo* during cold acclimation is of the moment conjectural; however, we will be concerned here with an examination of some of its properties and the response of these to the imposed stresses of cold acclimation and also to some extent, with treatment of the normal host animal with L-thyroxin. When given in physiological doses, thyroxin, in many respects (5, 6), produces metabolic changes similar to those in cold acclimation.

EXPERIMENTAL

Fractionation of tissues and conditions and methods of assay were as previously described (7). Details concerning new subfractions will be given as appears necessary for descriptive clarity at points where discussed. Cold-acclimated and thyroxin-treated animals used in this study were intact Long-Evans males, the latter injected daily for 14 days with 30 μg L-thyroxin in saline at pH 10. The cold-acclimated rats were exposed at cage temperature 6°C for not less than 45 days; they were individually caged under continuous room lighting. 'Controls' were similarly isolated but had low-level night light and room temperature of 24°C.

The use of 'kQ_{O_2}' and 'kP/O,' etc., to express the effect of fluff or other agents upon the metabolic activity of the mitochondria is an arbitrary empiricism. As applied to the data, it assumes the plot, log activity vs. amount of fluff added, to be a straight line, which in a limited sense is approximately the case. Since the kinetics of this relation are not yet worked out, the terms have

[1] This report is based on research supported by Research Grants C-3103 and C-3635 from the National Cancer Institute, National Institutes of Health, and in part by grants from the University of California Cancer Coordinating Committee and the American Cancer Society. The studies reported here derive from the joint efforts of a research team in which the author has enjoyed the effective support and collaboration of Dr. Alan S. Fairhurst, Dorothy J. Hoijer, Irene Rask, Jane C. Roberts and Satsuki Uyeno.

been applied purely for convenience. For a function such as P/O, which decreases with addition of the fluffy material, the k could be taken to be a rate constant expressing per cent of decay per unit of fluff N, and is easily computed simply as the quotient

$$(2.303(\log P/O_{M_2'} - \log P/O_{(M'_2+\text{fluff})})/\text{mg fluff N})$$

which has been done in this paper. However, for an activity which increases on addition of the agent, this logic does not apply, but a practical unit of specific activity may still be obtained from the quotient, and the positive sign used to denote stimulatory effects such as increases in Q_{O_2} or ATPase activity. This enjoys the didactic advantage of placing these activities in comparable units, the negative sign then being added to indicate that a function decreases with added agent.

RESULTS

As reported earlier (5, 8), well-washed mitochondria from liver fractions of cold and thyroxin-treated rats do not display the differences in P/O ratio observed with poorly washed preparations. Thus, further washing of the resuspended, once sedimented (M_1) to give (M_2) raises P/O and apparent Q_{O_2}, but does not wholly abolish the relative P/O depression in the cold series (table 1). However, the M'_2 (in which to the supernatant of the first extraction of homogenate are added the supernatant of one low-speed re-extraction of homogenate and the sedimentation of these at 25,000 G) shows essentially a

TABLE 1. *Comparative Responses of Rat Liver Mitochondrial Fractions Given Increasing Degrees of Washing*

Fraction	Series	Normal			Cold		
		Q_{O_2}	P/O	$\frac{+acc}{-acc}$	Q_{O_2}	P/O	$\frac{+acc}{-acc}$
M_1	453-70*	75.8	1.90	1.125	44.7*†	0.72†	0.907
	550-58	75.1	2.34	1.041	62.9	1.36	0.729†
	650-58	108.9	1.86	0.976	66.6	1.02	0.900‡
M_2	550-58	154.5	2.75	1.719	109.2	2.06	1.311
M'_2	668-74	161.5	3.00	2.147	207.9	2.78	1.784
	650-58	204.2	2.77	1.904	282.5‡	2.58‡	1.446§
M_w	676-87	290.4	3.32	3.098	308.1	3.20	2.663
	688-92	355.7	3.37	3.836	355.9‡	2.70	1.197§

Experimental conditions as in (2) and (7). Each series (from left to right) contained control and cold-acclimated animals in nearly equal numbers. The same series (reading down) indicates that identical animals furnish the different fractions. Thus, in *series 550–58*, 9 experiments were done, 5 on normal and 4 on cold-acclimated rats, with each rat contributing both an M_1 and an M_2 fraction. Q_{O_2} is in μl O_2/mg N of fraction/hr. The ratio (+acc/−acc) refers to Q_{O_2} in presence and absence of glucose-hexokinase trapping system (5). * Substrate, beta hydroxybutyrate (2); all others, alpha ketoglutarate (8). † Difference (normal-cold) $P < .05$. ‡ Data are for normal rats given 100 μg L-thyroxin/day (14 days). § Difference (normal-thyroxin) $P < .02$.

TABLE 2. *Effect of Albumen on M_1 Liver Mitochondria*

Albumen Added	Control			Thyroxine 30 μg/day × 14			Cold 102 days, 6°C		
	Q_{O_2}	Q_P	P/O	Q_{O_2}	Q_P	P/O	Q_{O_2}	Q_P	P/O
mg/flask									
0	139.2	17.8	1.44	113.2	4.73	0.48	92.0	9.1	1.11
2	130.4	17.5	1.50	103.2	4.43	0.49	93.7	6.7	0.79
4	125.4	15.3	1.31	89.2	4.58	0.57	83.9	10.3	1.38
6	—	—	—	—	—	—	80.2	8.1	1.13
8	103.6	14.4	1.57	77.6	4.55	0.66	—	—	—

theoretical P/O in both cold and normal systems, with Q_{O_2} not significantly depressed below that of the M_w fraction prepared by the Schneider method (9). The latter again shows no cold-induced depression of P/O. Thus, from table 1 it may be inferred that the depressant effects of either cold or thyroxin treatment on phosphorylation are largely removed by the second washing, since they do not appear in either M'_2 or M_w.

Reasons for this difference are therefore to be sought in activities or components eliminated by the washing procedure. The immediate inferences from such findings have been tested, namely that degradative activity such as that of ATPase, glucose 6-phosphatase, or other phosphatases could explain the differential phosphorylation in the M_1 fraction from the cold vs. normal. These now appear unlikely in view of the demonstrations that ATPase (Mg-activated) does not differ as measured either in the M_1 fraction (2) or in liver homogenate (10) and that net glucose 6-phosphatase activity remains unchanged if corrected for concurrent differences in endogenous phosphorylation (5, 7). The capacity of M_1 for aerobic glycolysis has also been superficially examined with the conclusion that this is not of the magnitude necessary for the differences observed in net oxidative phosphorylation; this needs further study, however.

Mitochrome activity (10a) was another possibility by which P/O of M_1 might be depressed in cold acclimation; this probability was minimized by experiments (table 2) in which varying amounts of bovine serum albumen (BSA) were added to the Warburg flasks containing M_1 mitochondria from normal, cold-acclimated and thyroxin-treated rats. While in all cases the Q_{O_2} of this fraction was increasingly depressed with increments of BSA, the P/O was not appreciably altered.

A reasonable inference may be drawn from the literature (11, 12) that the presence of microsomes in homogenates and crude residues therefrom would induce higher oxygen consumption without concurrent increase in phosphorylation. Thus microsomal elements induce DPNH oxidation *in vitro* without concurrent phosphorylation (13, cf. also 14). In any event it becomes evident that extramitochondrial components must be sought to account for these effects in the M_1 fraction.

Some further dissection of the fractions is achieved by isolation of the pink fluffy material which comes off with decantation of the supernatant and light surface washing

of the pellet; after this, the pellet may be resuspended as the M'_2 fraction. The fluffy material is sedimented by a 20-min. spin at 25,000 G, the supernatant carefully drawn off by syringe and the pink residue gently washed clear of the underlying small brownish residuum of mitochondria. The fluff from 10 gm of liver is then resuspended with 0.25 M sucrose to a volume of 5 ml and held at ice temperature for subsequent utilization.

Effects of the fluff suspension upon addition to M'_2 mitochondria are indicated in table 3. In the test systems where fluff is added to M'_2 mitochondria, the total nitrogen of the reconstituted system is approximately equal to that in the M_1. Addition of the fluff, however, raises Q_{O_2} relatively more than Q_P whence P/O decreases, but significantly so only in the systems to which is added fluff from cold-acclimated (or thyroxine-treated) animals. For the latter reason, the fluffy layer thus appeared a useful source from which to extend our information.

Sonic oscillation was applied to the fluffy layer at 0°–2°C (5 w. 9 kc) and the resulting material tested directly on normal mitochondria (M'_2). As this also showed characteristic depressive effects similar to those of the fluff, it was further separated by centrifugation at 144,000 G for 50 minutes into a sediment and supernatant; these also were active, but no more so than the original material, and prolonging of sonication beyond 10 minutes appeared to reduce this further.

As shown in table 4 the sediment of the 10-min. sonication had higher specific activity when derived from fluff of either cold-acclimated or thyroxin-treated rats than when taken from normal controls. In individual tests the sediment from thyroxin-treated rats (30 μg L-thyroxin/day for 14 days) frequently showed depressant effects upon both respiration and phosphorylation. The supernatant from the sonicated fluff has not been well studied, but when derived from cold-acclimated or thyroxin-treated animals and added to normal M'_2 mitochondria, it appeared to stimulate respiration and concurrently to depress phosphorylation; in this it resembled the fluff action and differed from the sediment which usually had either no effect or a depressant action on respiration.

TABLE 3. *Effect of Fluff from Normal and Cold-Acclimated Rats on Respiration and Phosphorylation of M'_2 Liver Mitochondria*

Fraction	Ser.	n	Animal Source		Q_{O_2}	kQ_{O_2}*	Q_P	P/O	kP/O*
			Mito.	Fluff					
M_1	18	3	Norm.		114.9		16.9	1.67	
		3	Cold		121.4		14.7	1.38	
M'_2	18	3	Norm.		242.8		46.0	2.04	
			Norm.	Norm.	417.4	1.288	76.3	1.89	−0.227
			Cold		207.9		43.8	2.21	
			Cold	Cold	395.3	1.473	54.1	1.55	−0.745†
M'_2	8	5	Norm.		305.1		76.8	2.82	
			Norm.	Norm.	389.2	0.448	68.4	2.00	−0.635
			Norm.	Cold	447.4	0.734†	61.0	1.62	−1.071†

Warburg system: fluid volume, 1 ml; medium (7); mg mitochondrial N per flask: M_1, ~0.75; M'_2, ~0.4; fluff N, ~0.4.
* See explanation in text. † Difference (normal − cold) significant at $P < 0.05$.

TABLE 4. *Effects of Addition of Sediment From 10′ Sonicated Fluff to Normal M'_2 Mitochondria, With and Without Bovine Serum Albumen Present*

n	Source of 10′ Sed.	Addition		Q_{O_2}	kQ_{O_2}	P/O	kP/O
		10′ Sed.	BSA				
2	Normal			292.4		2.67	
		+		296.4	0.043	2.36	−0.491
			+	317.7		2.14	
		+	+	285.2	−0.471	2.21	+0.173
4	Cold			292.6		2.64	
		+		298.1	+.079	2.38	−0.954
			+	283.3		2.634	
		+	+	267.1	−0.392	2.276	−0.757
2	Thyr.			330.2		2.54	
		+		365.8	0.462	1.40	−1.59
1	Thyr.			293.8		2.67	
		+		201.0	−1.54	2.11	−1.177
			+	310.8		2.42	
		+	+	244.3	−1.20	2.39	−0.064
1	Thyr.			315.2		2.76	
		+		336.0	+0.375	1.76	−2.770
			+	358.6		2.76	
		+	+	340.6	−0.320	2.38	−0.922

A useful criterion of the state of organization of the fractional components appears to be the sensitivity of the *in vitro* activity to added bovine serum albumen (BSA). This agent has been used in current work as a possible discriminator of the changing properties in various subfractions.

When BSA is added to the M'_2 mitochondria (table 5), no effects are observed on either P/O or respiration; however, BSA significantly lowers the Mg-activated ATPase of this fraction by about 25%, and when added to a system of M'_2 and fluff, depresses the fluff-stimulated increment of respiration, but fails to reverse the inhibitory effect of the fluff upon phosphorylation.

The relation between kP/O and ATPase activity needs further study; however, present data indicate that in systems with fluff added to M'_2, the kP/O is either not significantly correlated with the concurrent stimulation of ATPase activity, or in any case the correlation is negative. With further fractionation of the fluff, however, this relationship begins to change toward a positive correlation in which ATPase activity increases as depressive effects of the fluff-derived components upon phosphorylation increase. Thus, like the original fluff, the sediment of sonicated fluff increases ATPase activity of the M'_2 particles (i.e. from 12.7 to 28.9 μmole P/mg N/hr). However, the plot of P/O depressive activity

TABLE 5. *Effects of Bovine Serum Albumen (6 mg/ml) on Mitochondria (M'_2) in Presence of Fluff*

n	System		BSA	P/O	Q_{O_2}	Q_P	kP/O
	Mito.	Fluff					
5	Norm.		−	2.64	299.4	73.2	
	Norm.	Norm.	−	2.15	381.0	74.9	−0.403
	Norm.		+	3.27	277.0	79.2	
	Norm.	Norm.	+	2.38	300.2	64.0	−0.821
2	Norm.		−	2.98	375.8	100.5	
	Norm.	Thyrx	−	1.90	486.0	83.7	−1.045
	Norm.		+	3.08	351.8	97.1	
	Norm.	Thyrx	+	2.08	380.2	70.4	−0.807
1	Cold		−	2.31	287.0	59.1	
	Cold	Cold	−	1.08	413.2	38.1	−1.283
	Cold		+	2.36	252.1	52.0	
	Cold	Cold	+	1.194	285	30.1	−1.146

against ATPase stimulation (i.e. $-kP/O$ vs. kATPase) now shows a positive trend ($r = 0.62$) and the correlation is significant at $P < 0.02$. The effect of BSA addition to this system is to lower the above correlation to one which, though still positive, is not significantly greater than zero (i.e. $r = 0.26$; $0.10 > P > 0.05$). Whence BSA is at this stage beginning to counteract the activity of the fluff-derived agent.

In terms of the regression of $-kP/O$, (Y), on kATPase, (X), the equation of trend is, without added albumen,

$$Y = 1.21 + 0.4X$$

while with albumen added, the aggregate slope of all values is lowered to give,

$$Y = 0.59 + 0.23X$$

in which the slope is not significantly greater than zero.

Further fractionation of the fluffy material was carried out by resort to freezing and thawing the fluff suspension (four times) in ethyl ether at dry ice temperature. The extract was then dried on a steam bath under N_2 and stored overnight in vacuo; the weighed lipid was taken up in 10% ethanol-sucrose (0.25 M). The solutions were added to the fresh, ice-cold mitochondrial suspensions in 1:1 volume ratio just prior to introduction in the Warburg flasks. The concentration of ethanol was thus brought down from 10% to 5% by this initial mixing, whereafter 0.25 ml of the mixture was further diluted to 1 ml final volume of the flask, thus bringing the final ethanol concentration to 1.25%. Control flasks were charged with lipid-free ethanol-sucrose in the same manner.

In the course of the lipid studies control mitochondria were variously exposed to bovine serum albumen and ethanol-sucrose; hence it became relevant to know what specific effects these agents alone or combined might exert on the system. From the protocols a compilation of pertinent data permits the following statements: *a*) the Schneider M_w fraction appears not significantly affected by ethanol while respiration in both M'_2 and M_1 is mildly stimulated by it; *b*) BSA alone does not significantly alter respiration nor phosphorylation; however, *c*) when in combination with ethanol BSA enhances the respiratory effect significantly in both M_w and M'_2 fractions but depresses respiration of the M_1 with concurrent improvement of the P/O ratio; *d*) BSA (6 mg/ml) reduces ATPase activity about 25% in all three fractions.

Amounts of total lipid extracted from fluff by the present technique are slightly but not significantly greater in the cold-acclimated than in the control material; respective yields per mg fluff N were 0.73 and 0.59 mg dry lipid. When this lipid material is added to normal M'_2 mitochondria (table 6), it usually depresses both respira-

TABLE 6. *Comparison of Activity of Fluff and Fluff Lipid from Control, Cold-Acclimated and Thyroxin-Treated Rats, Added in Vitro to Normal M'_2 Mitochondria*

n	System*			Q_{O_2}	kQ_{O_2}	P/O	kP/O	Q_P
	Source	Fluff	Fluff lipid					
5	Normal			305		2.82		77
		+		389	+0.446	2.00	−0.635	68
				324		2.92		84
			+	288	−0.187	2.67	−0.140	69
5	Cold			305		2.82		77
		+		447	+0.726†	1.62	−1.071	61
				324		2.92		84
			+	268	−0.315	2.80	−0.039	66
4	Thyr.			265		2.83		66
			+	226	−0.381	2.03	−0.572	42

Warburg system: (in μmole/ml) ATP 2; alpha ketoglutarate 10; KF, 10; $MgCl_2$, 5; PO_4 as K_2H-KH_2PO_4, 15; Tris-HCl (pH 7.4) 25; glucose 25; hexokinase, Sigma IV 25 KM units. Mitochondria, 0.25 ml (~0.5 mgN) in 0.25 M sucrose premixed 1:1 with 10% ethanol-sucrose (all systems) for lipid carrier; final vol. 1 ml; incubation at 37° for 15 min., after 12 min. oxygenation and equilibration period. * Each of the *n* rats were used as donors for mitochondrial fluff of which part was used fresh on day 1 and the remainder extracted with ether and used on day 2 on mitochondria of *rat 3* etc. † Significantly greater than corresponding normal ($P < .02$).

TABLE 7. *Assay Data (in % of Total Recovery) Obtained by Silicic Acid Column Separation of Fluff Lipid From Normal, Cold-Acclimated and Thyroxin-Treated Rats*

Subgroup	Control	Cold	Thyroxin
Sterol Esters	1.5	4.4	6.1
Triglycerides and F.A.	18.9	28.2	16.3
Free sterol	15.1	20.6	18.0
Diglyceride	2.8	0.7	1.8
Monoglyceride	19.4	2.1	3.4
Phospholipids	43.3	43.9	54.4
lipid (*mg*) on column	74.1	81.7	99.3
lipid (*mg*) off column	74.9	80.1	108.6
% recovery	101.1	98.0	109.4

tion and phosphorylation, depressing the latter enough to reduce the P/O appreciably. The fluff, however, has a similar depressant effect on phosphorylation but associated with it is a substantial stimulation of respiration; the resulting effect on P/O is thus much more pronounced. These results suggest that respiratory control is here being uncoupled from phosphorylation by an agent in the fluff which is not found in the lipid extract. The fact—that respiration of the M_1 system from the cold animals is characteristically depressed in the manner observed with the lipid addition—argued in favor of further study of the latter, rather than extending the work on the respiratory stimulating effect.

The lipid obtained from fluff by the cold ether extraction procedure outlined earlier was subfractionated on silicic acid columns according to the methods of Mead (15). This procedure gave quantitative yields of 6 groups of fatty acids (table 7). Notably, the distribution of lipids appeared quite similar in the cold- and thyroxin-treated rats; these exhibited somewhat higher sterol ester levels than did the controls and a markedly lower level of monoglycerides.

These lipid subfractions were then added (in ethanol-sucrose) as before to the mitochondria for assay of biologic activity, employing in this instance the Schneider, M_w, liver mitochondrial fraction from normal rats (table 8). Respiratory stimulation was observed in the controls only on addition of the phospholipids and the free and esterified sterols, and the latter only from the control fluff; with these exceptions, all other components inhibited both respiration and phosphorylation to varying degrees.

A most interesting shift is noted in the effects on phosphorylation, from a high inhibitory effect of the phos-

TABLE 8. *Effects on Respiration and Phosphorylation of Lipid Fractions Added to M_w of Normal Animals*

Source of Lipid		None	Phospholipid	Sterol (Free)	Sterol (Ester)	Glycerides		
						Tri-	Di-	Mono-
Normal	Q_{O_2}	304.52	393.87	330.15	353.17	275.0	264.61	354.29
	kQ_{O_2}		+0.494	+0.786	+4.145	−0.525	−2.239	+0.161
	Q_P	77.69	11.076	18.34	84.59	41.51	67.14	60.77
	P/O	2.980	0.299	0.613	2.691	1.774	2.914	1.926
	kP/O		−2.859	−5.555	−3.713	−1.400	−0.706	−0.886
Cold	Q_{O_2}	328.53	389.18	350.30	155.14	273.15	259.64	226.82
	kQ_{O_2}		+0.688	+0.618	−3.036	−0.485	−2.756	−2.267
	Q_P	81.34	35.84	47.80	30.15	20.17	55.17	31.99
	P/O	2.802	1.323	1.381	1.585	0.801	2.380	1.375
	kP/O		−3.412	−2.042	−2.421	−3.908	−1.563	−3.946
Thyroxine	Q_{O_2}	347.81	371.48	395.92	180.93	224.0	387.27	283.35
	kQ_{O_2}		+0.144	+0.345	−1.220	−2.109	−0.222	−0.964
	Q_P	84.55	47.28	43.79	7.186	31.33	10.041	19.89
	P/O	2.754	1.428	1.257	0.440	1.349	0.974	0.794
	kP/O		−1.423	−2.124	−2.541	−5.150	−4.411	−2.937

TABLE 9. *Effect of BSA on Activities* of Lipid Fractions From Normal and Cold-Acclimated Rats*

Exper. No.	Q_{O_2}	Q_P	P/O	Fraction Tested	BSA	P/O	Q_{O_2}	Q_P	kP/O
				Control					
1	245.5	67.6	3.098	Phospholipid	−	0.428	432.2	16.5	−2.933
1	358.1	100.2	3.184	Phospholipid	+	3.060	372.5	101.7	−0.059
1	245.5	67.6	3.098	Free sterol	−	0.736	354.7	23.3	−6.177
1	358.1	100.2	3.184	Free sterol	+	3.555	225.4	78.5	+0.463
2	356.8	84.5	2.668	Triglyceride	−	1.973	227.2	44.6	−1.395
2	375.8	100.8	3.034	Triglyceride	+	3.076	295.1	80.5	+0.043
2	356.8	84.5	2.668	Monoglyceride	−	2.041	362.4	65.7	−0.772
2	375.8	100.8	3.034	Monoglyceride	+	2.914	272.9	70.8	−0.116
				Cold-Acclimated					
4	299.0	71.1	2.722	Phospholipid	−	0.495	522.1	23.0	−5.608
4	348.8	87.6	2.823	Phospholipid	+	2.649	367.1	86.4	−0.209
3	392.4	88.8	2.569	Free sterol	−	0.259	303.7	7.0	−2.901
3	456.8	114.3	2.804	Free sterol	+	2.770	370.1	32.0	−0.015
3	392.4	88.8	2.569	Triglyceride	−	0.467	248.8	10.1	−3.748
3	456.8	114.3	2.804	Triglyceride	+	3.127	116.5	28.4	+0.240

* Tested against normal M_w mitochondria with and without presence of 6 mg BSA/ml.

pholipids and sterols from control animals to one much lowered in the cold and thyroxin groups. The converse obtains with respect to the glycerides, where greatest activity appears in extracts from thyroxin-treated and cold-acclimated rats.

Table 9 furnishes details of the protective action which BSA exerts upon the depressant effects of these lipid fractions on normal M_w mitochondria. From this it becomes wholly evident that one may assume this action to indicate a much simplified order of complexity in the effective agents involved. This is demonstrative of a binding effect between the albumen and the lipid moieties here involved. Obviously we have reached at this point a new order of regulatory potential, which may only have its role in this *in vitro* system. However, it is possible that this very mechanism is in some degree responsible for a measure of the metabolic control of this system by the various agents which control the release of fatty acids in the course of the normal response to the cold stress.

As a closing note it should also be added that since the lipid fractions show very high ATPase activation, the correlation between this and $-k$P/O for these components approaches unity. The regulatory significance of this has still to be evaluated in terms of the various protective mechanisms inherent in the extramitochondrial cytoplasm.

SUMMARY

The depression of oxidative phosphorylation observed in mitochondrial preparations from livers of either cold-acclimated or thyroxin-treated rats appears partly to depend upon the presence of extramitochondrial factors which are removed on further washing. These factors are demonstrable in the pink fluffy layer, and in either this stage or the admixed one preceding this, they are largely insensitive to the addition of bovine serum albumen. At these stages the depressive effects on phosphorylation appear unrelated to relative ATPase and glucose-6 phosphatase activities. Sonic oscillation of the fluff or a crude lipid derived by cold ether extraction, both yield factors which though strongly inhibitory of phosphorylation, also become more sensitive to reversal by BSA. These subfractions may exert their degradative effects at least partly through ATPase activation, since the depressive effects on P/O became more highly correlated with ATPase activity as structural complexity was reduced. The ether-soluble lipid from fluff of cold-acclimated and thyroxin-treated animals was resolved on silicic acid columns into six groups of fatty acids, among which the monoglycerides appeared lower than in the normal animals and the sterol esters higher. The triglyceride fraction (including other fatty acids) was also higher in cold than normal animals, and like the mono- and diglycerides showed a higher specific activity in depressing P/O than when from control animals. These effects and those of the other fatty acid fractions involved strong ATPase activation and were universally sensitive to reversal either in whole or in part by addition of 6 mg BSA/ml.

It appears likely that *in vivo* some extramitochondrial phosphorylative control may reside in a lipoproteinoid material which serves to bind or stabilize fatty acids and possibly to moderate their topical effects upon the mitochondria.

REFERENCES

1. Smith, R. E. and A. S. Fairhurst. *Fed. Proc.* 17: 151, 1958.
2. Smith, R. E. and A. S. Fairhurst. *Proc. Natl. Acad. Sci. U.S.* 44: 705, 1958.
3. Panagos, S., R. E. Beyer and E. J. Masoro. *Biochim. et biophys. acta* 29: 204, 1958.
4. Hannon, J. P. *Fed. Proc.* 17: 1070, 1958.
5. Smith, R. E. (This Symposium) *Fed. Proc.* 19, Suppl. 5: 64, 1960.
6. You, R. W. and E. A. Sellers. *Endocrinol.* 49: 374, 1951.
7. Fairhurst, A. S., J. C. Roberts and R. E. Smith. *Am. J. Physiol.* 197: 370, 1959.
8. Smith, R. E. and A. S. Fairhurst. *Fed. Proc.* 18: 148, 1959.
9. Schneider, W. C. *J. Biol. Chem.* 176: 259, 1948.
10. Hannon, J. P. and D. A. Vaughan. *Am. J. Physiol.* 198: 375, 1960.
10a. Polis, B. D. and H. W. Schmukler. *J. Biol. Chem.* 227: 419, 1957.
11. Siekewitz, P. *J. Biol. Chem.* 195: 549, 1952.
12. Lehninger, A. L. *J. Biol. Chem.* 190: 345, 1951.
13. Krisch, K. and K. J. Staudinger. *Biochem. Ztschr.* 331: 195, 1959.
14. Schneider, W. C. *Advances in Enzymol.* 21: 1, 1959.
15. Mead, J. F., W. H. Slatan and A. B. Decker. *J. Biol. Chem.* 218: 401, 1956.

Cellular and subcellular energetics

Summary

ROBERT E. SMITH
Department of Physiology, University of California School of Medicine, Los Angeles, California

THE INCREASED OXYGEN UPTAKE found in acclimation to cold is an easily measured indication of greater utilization of substrate for the production of heat and transfer of energy. This has been established in whole animals and in surviving tissues, homogenates and various mitochondrial preparations. The work of Dr. Weiss has alerted us to some interesting considerations in the use of these measurements as an index of adaptive processes. The age of the animal must be considered as an additional variant to cold. The very young animal does not alter its hormonal response patterns sufficiently to survive (1), and the animals beyond a certain age show a decreased ability to compensate for heat loss. It is of note that the liver, which is most commonly chosen for experimental purposes, continues to respond to cold stimulation longer than do the other tissues.

The role of thyroxine in cold acclimation has been given added significance by the demonstration that injection of this hormone assures the survival of aged rats and those subjected to the double stress of cold and clipping.

These results of Dr. Weiss and related studies by Dr. Hannon and others raise the question as to whether acclimation should be defined as specifically applying to the peak of accelerated metabolic activities that occurs at 2–5 weeks in the rat exposed at 2°–5° or at a later period where plateau values are well above normal, but lower than the peak. The wide variation in results of various workers is evidently ascribable in part to variance in respect both to age and the time-intensity conditions of exposure as well as diet, breed and other factors often uncontrolled.

Concerning biochemical changes, Dr. Hannon has reported that a period of 1 month in the cold at 5°C produces elevated blood nonprotein nitrogen and increased urinary nitrogen. Phospholipids, cholesterols and ketone bodies are increased at this time, and the turnover rate of blood sugar is increased above the normal. These findings all indicate an increased utilization of substrate with increased oxygen uptake and concomitant changes in the enzyme systems.

Among the latter are increases in activities of succinic dehydrogenase and its complex, and in cytochrome oxidase, the relative rise being much higher in muscle than in liver. Malic oxidase and the dehydrogenase also increase in both tissues while lactic dehydrogenase may not. Concurrently no change is detectable in the activity levels of DPNH cytochrome *c* reductase. These findings by Dr. Hannon are noted to be confirmatory of the earlier studies of You and Sellers (2) and of Clark *et al.* (3) in respect to succinic oxidase and the succinic dehydrogenase complex in skin and liver. Likewise they agree with the reports from the laboratory of the present reviewer (4) regarding lack of cold effects on DPNH cytochrome *c* reductase of rat liver; additionally Smith and Fairhurst (5) had earlier found in liver no changes in TPNH cytochrome *c* reductase nor in the TPNH-dependent dehydrogenases of glucose-6 phosphate and 6-phosphogluconate. These authors also reported small but insignificant changes in DPN-TPNH transhydrogenase of liver particulates from cold-acclimated rats.

These apparently negative findings are of particular interest in view of the clearly demonstrated effects of thyroxin and thyroid hormone on these same enzymes in related studies by the same workers and others as well. To this extent the thyroxin-treated rat does not appear analogous to the cold-acclimated one.

In Dr. Hannon's study the observed enzyme changes evidently involve increases in enzyme amount as well as specific activity. He conjectures that this activity may connote an increase in size and/or number of mitochondria, or a physical alteration of the mitochondrial structure of such a nature as to make the enzymes more available to substrate. The thyroxine effect has been thought to be ascribable in part to a change in permeability of the mitochondrial membrane structure.

However induced, respiratory regulation within the cell is clearly of prime significance to the over-all energy exchange in cold acclimation. While several specific mechanisms have been discussed or mentioned during the course of this Symposium, no definitive conclusions appear warranted. We are presently aware that respiratory control in general may be effected by alterations either in *1*) the metabolic pathways normally leading to

energy storage through phosphorylation or 2) oxidative pathways not giving rise to phosphorylation. The latter include those mediated by various aerobic dehydrogenases and the copper-containing oxidases, and normally respond to substrate addition by corresponding increases in oxidative metabolism. Enzymes included in this category are flavoprotein-linked and all are capable of transferring electrons directly to molecular oxygen. The group includes the L- and D- amino acid oxidases, glycine oxidase and the autoxidizable flavoproteins such as dopa-oxidase, tyrosinase and ascorbic acid oxidase (cf. 6). A review of the specific actions of these enzymes will disclose that in cold acclimation their roles may become especially important in relation to the enchanced substrate turnover and particularly in reference to the metabolic functions of ascorbic acid and the catecholamines as outlined elsewhere in this Symposium. In specific reference to heat production, it is important to note that the energy released via these pathways is evidently not conserved by the cell and hence becomes immediately available as heat.

The alternative mechanisms of respiratory control, i.e. that proceeding normally to phosphorylation via the cytochrome system, has received somewhat more attention in the current Symposium; this is understandable and reasonable in view of its predominant role in the gross metabolic energy exchange. Moreover, we have as a group been intrigued with the notion that in cold acclimation an uncoupling of oxidative phosphorylation could serve at once both the facts of respiratory enhancement and the increased demand for heat per se. However, this is by no means an impelling motive, since alternative explanations may be offered in terms of adaptive changes permitting greater net oxidative turnover with appropriate shifts in the neurohumoral regulatory pattern. Respiratory control through the phosphorylating pathways nonetheless does differ from that via the aerobic dehydrogenases in that simple additive increase of substrate will not necessarily increase respiratory rate, since the limiting factors normally lie in the coupling of respiration to phosphorylation, rather than in substrate availability. In this the respiratory rate becomes proportional to ADP level and thus is generally increased by factors which either degrade ATP (e.g. ATPase) to ADP or generate ADP by other means (e.g. myokinase, creatine phosphate synthesis reactions).

When hexokinase and glucose are added to the *in vitro* system, containing substrate, phosphate and ATP, ADP is generated as phosphate is cycled through ATP to form the stable glucose-6-phosphate, and the respiration is usually somewhat stimulated. The extent of this stimulation is consistently greater in washed liver mitochondria (but less so in homogenates or unwashed mitochondria) from normal rats than with those from cold-acclimated or thyroxin-treated rats. The assumption here is that prior to addition of the hexokinase trap the rate of ADP generation in each system is proceeding at less than the maximal rate, to which it is subsequently driven by the trapping system. As the respiration of the thyroxin-treated and cold-acclimated systems is at a basal rate higher than the normal, the rise induced by the trap is therefore less. Consistent with this is the higher level of endogenous hexokinase activity found in the liver of the cold-acclimated rat. To the same end, the increases noted earlier in respect to the anaerobic dehydrogenases and their oxidase systems, along with the raised levels of coenzyme A (cf. J. Campbell *et al.*, this Symposium (7)), suggest that ADP generation is high and hence probably not the rate-limiting factor in the respiration of the liver in cold-acclimated rats. Likewise in muscle, the rise in malic dehydrogenase plus the elevated turnover of creatine phosphate at the expense of ATP would appear to support a similar conclusion. Conversely, this circumstance would be expected to facilitate maintenance of the higher level of respiration observed in the cold acclimated state.

Inferentially, the rate-limiting steps must be sought in the electron transfer chain where the higher oxidation rates in cold acclimation appear to involve varying degrees of uncoupling of oxidative phosphorylation, activation of latent enzyme activity and absolute increases in the concentrations of certain of the anaerobic dehydrogenases as noted above (cf. J. P. Hannon and R. E. Beyer, this Symposium (8, 9)).

Several lines of evidence have been adduced to indicate the operation of thyroxine as a moderator of electron transport in cold acclimation. Thus Panagos and Beyer (10) related the decrease of opacity of rat liver mitochondria to a concurrent fall in oxidative phosphorylation, beginning within the first 2 weeks of exposure to cold. In substance, this has been confirmed in both cold and thyroxin-treated rats (cf. R. E. Smith, this Symposium (4)) and, with respect to thyroxin effects, extensively studied in several laboratories during recent years.

In well-washed liver mitochondria from cold-acclimated rats the initial optical density at 520 mμ is not greatly depressed below normal, and though respiration may be somewhat elevated there is no significant change in P/O ratio. Under these conditions the most consistent observation is the lower respiratory response of the cold-acclimated system to the addition of the hexokinase-glucose acceptor. From these data it is possible to infer the presence in cold acclimation of an incipient state of uncoupling of oxidative phosphorylation within the liver, which may also be associated with structural alterations of mitochondria *in situ*.

As one permits more extramitochondrial admixture to the liver mitochondrial particles, the P/O becomes clearly depressed, the cold-acclimated preparations more so than the normal; this depression may or may not be associated with changes in respiration. Among the factors contributory to the depression of P/O in both thyroxine-treated and in cold-acclimated rats, is

a poorly characterized material (probably a complex lipoprotein) identified with the pink fluffy layer of the mitochondria (cf. 4). When added to normal liver mitochondria, fluff from cold animals shows greater specific activity than that from controls.

The fluffy material has not yet been successfully solubilized; while a cold-ether-extractable lipid and fatty acid subfractions thereof are all effective in depressing phosphorylation, the latter effect is reversible by bovine serum albumen, whereas the original fluff effect is not. These and related results, however, may indicate that lipids and possibly fatty acids do in some manner serve to moderate oxidative phosphorylation *in vivo*.

A number of papers in this Symposium have elucidated upon the labilization in fatty acid transport which occurs in response to the cold stress; aside from their pertinence to the above considerations, these effects may well relate to the target action of norepinephrine demonstrated by Dr. Depocas' careful study of the cold-acclimated, functionally eviscerated rat.

Other means have been considered by which P/O might be altered during cold acclimation. Of these the most discussed has been the possibility of preferential employment of TPN-dependent pathways. While evidence for this is highly suggestive, current data on the cold-acclimated state do not appear sufficient to confirm its role in this respect. The interesting possibility that ascorbic acid may serve the dual role of hydrogen donor through a nonphosphorylating pathway to O_2 as well as that of a shunt through cytochrome b_5 (cf. D. J. Hoijer, this Symposium (11)) would also provide a pathway of lowered phosphorylative efficiency. Finally, the preferential use of succinate or succinyl CoA as suggested by available data would again reduce ATP yield per mole of oxygen.

REFERENCES

1. McCance, R. A. and E. M. Widdowson. *J. Physiol.* 147: 124, 1959.
2. You, R. W. and E. A. Sellers. *Endocrinology* 49: 374, 1951.
3. Clark, R. T., H. I. Chinn, J. A. Ellis, N. E. R. Pawel and D. Criscuolo. *Am. J. Physiol.* 177: 207, 1954.
4. Smith, R. E. (This Symposium) *Fed. Proc.* 19, Suppl. 5: 64, 1960.
5. Smith, R. E. and A. S. Fairhurst. *Fed. Proc.* 17: 151, 1958.
6. White, A., P. Handler, E. L. Smith and DeW. Stetten. *Principles of Biochemistry*, 2nd ed. New York: McGraw-Hill, 1959.
7. Campbell, J., G. R. Green, E. Schönbaum and H. Socol. (This Symposium) *Fed. Proc.* 19, Suppl. 5: 124, 1960.
8. Hannon, J. P. (This Symposium) *Fed. Proc.* Suppl. 5: 139, 1960.
9. Beyer, R. E. (This Symposium) *Fed. Proc.* Suppl. 5: 145, 1960.
10. Panagos, S. and R. E. Beyer. *Fed. Proc.* 17: 121, 1958.
11. Hoijer, Dorothy J. (This Symposium) *Fed. Proc.* 19, Suppl. 5: 90, 1960.

VI

General Discussion and Summary of the Symposium

Chairman: FRANK FREMONT-SMITH

General discussion

E. F. ADOLPH, L. IRVING, O. G. EDHOLM, J. S. HART, L. D. CARLSON, F. FREMONT-SMITH, MERVA COTTLE, K. M. KNIGGE, O. HEROUX, A. D. KELLER, E. SCHÖNBAUM, D. J. HOIJER, S. A. D'ANGELO, I. G. FLETCHER, E. J. MASORO

Coordinators: E. F. ADOLPH, J. S. HART, R. E. SMITH

DR. FREMONT-SMITH: Fortunately I do not have the difficult task of summarizing a meeting of this sort, because as chairman I have appointed three subchairmen to do the summarizing for me. And they, in turn, have been wise enough to appoint sub-subchairmen to do the job for them. This will lead to some spontaneity I hope. Gentlemen, I now turn the meeting over to the first subchairman, Dr. Adolph.

DR. ADOLPH: I would like first to make a few general statements in the hope that some of these will represent outcomes of our previous deliberations. When I think of what an adaptation is, I am sure it is some sort of response; and any response calls forth, in a physiologist, a picture of some reflex setup. There is a sensory spot, a communication apparatus and an effector of some sort. Sometimes these are all wrapped up in one mitochondrion, but we usually work first with those which are spatially separated. We have done a great deal of talking about the mediators or communication systems in connection with what we call adaptations. We have not done very much with the effector equipment. We have named muscles and liver, and even they are rather nonspecific. We have done still less with the sensory aspects of these adaptive reorganizations or modifications. Some of us, however, have been anxious to localize the origin of sensations, perhaps in the hypothalamus, whereby the organism as a whole responds to some particular stimulus. But since we have not agreed on where such a single sensory spot might be, the chances are that there are many such places and that the responses are multiple, with some sort of a scanning device by which these various sensory inputs are coordinated to give a somewhat unified result in the organism.

Personally, I think of physiological adaptations in terms of physiological regulators. When we come to heat regulation, we recognize that the most typical or the most extreme examples of regulation of body heat are limited to a very few kinds of animals. We often think of birds and mammals as the only ones concerned with such regulation of heat, but we must recognize that heat adaptation is not equally developed in all phyla, mainly because very special processes and structures are concerned in the regulation of heat and in the adaptation to heat and cold. These regulatory and adaptive arrangements are part and parcel of the whole, and we cannot possibly say where regulations start or where adaptations begin; they are all degrees of the same total mechanism.

This raises the further question as to how specific are these adaptations of which we speak. Once or twice in our discussions the question has come up: is adaptation to cold identical with adaptation to low oxygen or with adaptation to heat, or are they antagonistic to one another? It is surprising how little has been done to see whether one adaptation is compatible with another. The data that exist, so far as I can assess them, show that there is relatively little overlap between various forms of adaptation. Indeed there is some evidence of antagonism between one type of adaptation and another. I do not think it is by any means proved that an animal cannot be simultaneously adapted in part both to heat and to cold. You can think of an organism as continually seesawing in response to the various environmental influences to which it is exposed. And since no organism is influenced a hundred per cent only by the cold aspects of the environment, obviously there are bound to be various combinations or degrees of adaptation to various types of influences. This may seem to some of you a hopeless way of talking about organisms. All of us would like a scheme whereby we could define cold adaptation in quantitative terms independently of all

the other adaptations and environmental influences to which an organism is subjected, but I suspect that this may be hoping too much.

I am sure that there are varieties of cold adaptation itself. We cannot talk about cold adaptation as being a unitary thing. There are different varieties not only among species or among individuals but also within the same organism; at different times there can be different degrees of each factor in the syndrome. Maybe we should say there are several syndromes of cold adaptation and not just one. From this point of view we can look forward to considerably more research, since we have not gotten very far in describing even one syndrome of cold adaptation.

Another point on which I would like to remark is that adaptation, as we are talking about it in terms of the modification of the organism, is more than energetics. When we talk about heat or cold, we say heat is a form of energy and we ought primarily to think in terms of energetics; but obviously there is so much more to cold adaptation than simply a shift in energy exchanges. Vasomotor responses, piloerector responses, postural responses, fat deposition and the sensory adjustments all call for a comprehensive idea about adaptation.

We have a lot to think about if we try to contrast our knowledge of adaptation to cold with our knowledge of adaptation to heat. Historically, we knew about the adaptation to heat before we knew about adaptation to cold. I would say that heat adaptation was partially understood around 1900, and earlier observations showed such a thing existed. With just a thermometer one could show that an organism did not heat up so much after a few days of heat exposure as it did the first day; with intermittent exposures, the exposures became less and less taxing. It is also interesting that we knew a lot about heat adaptation in man before we knew much about heat adaptation in other mammals. It has been the converse in the study of adaptations to cold. We knew a lot about rats and some other small animals before we were sure that there was a human adaptation to cold. And some of us, as you heard last evening, are not sure even now that such an adaptation does occur in man. One can suppose that the study of adaptation to heat was a more practical problem, with a greater demand that physiologists find out something about organisms exposed to heat. I do not believe this is true; at least as many people have been killed by overexposure to cold as by overexposure to heat.

I would like again to stress the species differences in cold adaptation and to point out that the same individual, repeatedly exposed, does not always respond in the same way. An organism may have a galaxy of responses that can be called upon. What determines which of that galaxy it will put into operation? We have some evidence that there might be a choice among the different ways of combating the cooling effect, and if one does not work, others may be put into operation. I cannot point out any specific instances where this priority system operates, but I have the notion that there is a priority system for each organism at each exposure. An organism is not choosing between survival and nonsurvival in most of the adaptations which we have discussed; rather it is choosing between some one form of attaining a steady state in relation to its environment as opposed to some other form. This again emphasizes that we should perhaps acquire more information about the establishment of steady or stationary states and not be satisfied with the initial responses of an organism after a brief exposure.

Considering the huge contrast between our knowledge of rats and what we know about men during cold adaptation, I suggest we have two echelons of biochemists, one of them working on men; soon we would really know something about human adaptation to cold in a chemical fashion. It is true that most of us will not give up our tissues for homogenization, but most of us would be willing to give samples of blood; the biochemists learn a great deal about the tissues by an examination of the blood. With all the micro- and ultramicromethods available, we should not object to giving some biopsy samples, especially for the ultramicroscope or the electron microscope. We would have to sacrifice only a few cells to the biochemist.

One other point of discussion was the attempt to divide the responses of adaptation into nervous and nonnervous responses. Some were willing to say that nonnervous responses are hormonal responses. It seems to me that there are many responses which do not fit into either category and we cannot think only in terms of the mediators by which responses are aroused. I am sure that, as Szent-Gyorgy said, each cell leads a private as well as a public life, and that if we can think of each cell as having its own response methods as well as a response for the general economy of the organism, I think we may have a greater appreciation of what is involved in adaptation and particularly in cold adaptations. So I do not think adaptations are limited to any set of categories that we have been trying to divide them into; I hope that by recognizing more categories we can be a little more comprehensive in our notions.

We, of course, all assume that these adaptations are preformed and that when somewhing presses the trigger the response unfolds. But there may also be provision for exploration of several possibilities. This may mean that there is no artificial substitute trigger of an adaptation. There has been an undercurrent of thought to the effect that all you have to do is find a hormone or a nerve fiber or a sensory spot which has to be stimulated in order that the whole syndrome of cold adaptation will unfold. I see little hope that this is going to be the case; in fact, I would think it is a poorly constructed organism which makes all of its responses dependent upon one trigger. I would expect, if an organism is anything like I think it is, that there are many triggers, many communication systems and many types of responses, and that we will never be able to substitute for a cold exposure a single stimulation from a drug or a hormone or a nerve impulse. I hope I am wrong for the

benefit of those of you who feel that you are making progress by looking for that trigger.

I would like to acknowledge the fact that my concepts of physiological adaptations have evolved over the years and I hope that they will keep on evolving. There is little use in thinking that one has to be fully consistent or has to defend a point of view; we are working in a branch of physiology which is probably evolving faster than most.

DR. IRVING: Of course, I did not expect to be called upon to speak, but I happen to have a manuscript in my pocket and a lot of slides. It seems to me that further provocation is needed to bring folks up on their feet and I'm reminded of the situation which philosophical physicists reach in the third or fourth chapter of their books, when they begin to wonder if it is possible to make experiments upon any function or system within the universe without the means of measurement distorting the function to be measured. And then they go further and say, well, it's not possible to experiment without distorting the systems, and it's probably not even possible to look at them without some bias. Whereupon they reach the comfortable reflection that the best thing to do is to sit and think critically about the predicament, for that creates but little disturbance. Now we physiologists have a prime set of examples of natural systems distorted by experimentation, for the animals which we would adapt to cold are subjected to some extraordinary disturbances. We grasp them more or less firmly, according to their size and their savageness, and thrust them into a cold room, and keep them there for an arbitrary period of time. We then carry on various observations on them which may go as far as putting them through a blender and reducing them to an homogenate. There is some disturbance of the system, and yet I do not object to that when I can see that out of the homogenate, or from the information derived through observing it, we can get back toward a resolution of those systems and functions and materials as they might reasonably have been associated in the living animal.

We are dealing with living animals, and by calling the influence which we are imposing upon them acclimatization, or acclimation, or adaptation, we are subjecting them to some alteration of their surroundings which resembles exposure to a natural set of conditions. I believe we should consider whether or not the conditions imposed upon the animal, in order to bring about a change from its supposed initial state, are truly referable to the normal environmental conditions which are described under the terms 'acclimation' or 'adaptation.' We have seen some recent demonstrations from Sandy Hart's laboratory, particularly nice because they agree with some suspicions which I have long had about thrusting a rat for 6 weeks into a cold chamber and causing elevation of its basal metabolism. If Hart exposed the white rat to the natural cycle of the seasons out of doors, he found that in winter the rat soon passed through the type of acclimatization changes which were observed after 6 weeks of exposure in the cold room. The changes then progressed to another state in which the basal metabolic rate was not elevated and in which the capability of the animal to react metabolically to cold was much increased. So I submit that the arbitrary subjection of a white rat to a period of 6 weeks of exposure may not have brought it to a steady state which could be recognized as a part of acclimation.

Often by selecting animals which are naturally capable of making very considerable alterations of an apparently adaptive nature, one can enlarge the dimensions which are to be viewed and one can feel sure that he is observing the process which is called acclimation or a type of adaptation. And further, we note from experience that the development of adaptability to its full extent by natural experience or proper training commonly brings out, in a sample of animals, a uniformity in the reactions characteristic of the population. So I suggest that some of these analyses which prove to be so extraordinarily interesting in reference to the processes of acclimation and adaptation might be advanced faster by using selected animal populations of the most favorable type and by treating them in such fashion as to secure the full expression of their adaptability. Great advantages can be derived from work with human and animal populations which are truly homogeneous in regard to their essential individual nature, their background and experience, and in which homogeneous reactions will probably demonstrate biological adaptation.

DR. EDHOLM: I've derived great benefit from coming to this congress, and particularly in learning so much in the field of intermediary metabolism; however, I feel that the biochemists will gain something by looking at the whole animal. It is essential that there should be a number of biologists who are prepared to do this. This meeting provides an opportunity for those working either with the whole animal or intensively on particular aspects of metabolism to compare views and to arrive at an integration of interpretations. Temperature is an essential parameter in any biological process, but only in recent years has it received detailed attention, and many physiologists are still not sufficiently aware of its importance. This conference has demonstrated very clearly how essential the effects of temperature are, and how necessary it is to keep the whole animal in mind.

DR. HART: This impressive Symposium has brought forth a great many concepts and ideas. If there is any regret that we can express now it is perhaps that we have heard a great deal and have not had quite enough time to talk about it. Therefore we hope that this afternoon can be devoted to a spontaneous discussion of specific items in the previous sessions and that an open exchange of views may result. I have been aided by the previous speakers who have been able to generalize on one or two subjects of great interest to me. One of these in particular, the subject that Dr. Irving has mentioned,

is the need to look at different species in nature, to observe their response to their natural environment and to compare these adjustments with those we observe in response to single factor or multifactor changes in the laboratory. We can learn a great deal about the whole processes of adaptation by this survey, not only from ecological considerations, but also from contrasting the mechanisms of cold adaptation in nature and in the laboratory. Laboratory responses of animals to cold must have their counterpart in nature, but we have not really seen how this operates. In particular, we are uncertain if the phenomenon of metabolic acclimation, described for the white rat, is of general occurrence in wild species acclimatizing to winter. The application of certain aspects of cold acclimation, e.g. nonshivering thermogenesis, remains to be demonstrated for naturally occurring species. How general is this phenomenon? I will pose this question with the hope that it will be answered in the future.

My focus on the applicability of acclimation phenomena to animals in nature is perhaps viewing the macrocosm when we do not fully understand the microcosm of temperature acclimation in any species. For most of us here, the mechanism of metabolic acclimation to cold is the main theme, and it is this which we will undoubtedly continue to discuss. I will start with one aspect that has greatly intrigued some of us, viz. the problem of the tissues responsible for elevated heat production in the cold when shivering is not involved. An understanding of the physiological and biochemical mechanisms of cold acclimation must have as a necessary prerequisite a knowledge of the tissues in which nonshivering thermogenesis occurs since the latter seems to be a feature of such fundamental importance in the acclimation process. Dr. Depocas and others have been able to summarize some of the information on this question, but unfortunately there was insufficient time for discussion of the topic. I would therefore like to call on one or two people to give us their views on the source and neurohumoral control of nonshivering heat production. Dr. Carlson, would you care to follow up with some of your ideas on this very important aspect of metabolism?

Dr. Carlson: I would like, by means of some comparisons and examples, to suggest a change in the emphasis that has been made by previous speakers. We have an understanding of sickle cell anemia, not because of studies on the whole man but because of evidence from electron micrography and physical biochemistry. Certain hereditary diseases are clearly understood when the biochemistry of the disease is known. Thus we need to search for ultimate mechanisms and I think previous speakers have been making a plea for synthesis—the integration of these mechanisms into the whole reaction with proper emphasis on the functional mechanism. Nonshivering thermogenesis is a case in point. If we had not been probing for mechanisms of calorigenesis in cold-acclimated animals we should not have discovered nonshivering thermogenesis. Once this discovery is made the previous temperature history of an animal, as well as its present body temperature, has a far-reaching influence, whether or not the experimenter is investigating neurophysiological, cardiovascular or other phenomena.

With respect to nonshivering thermogenesis, I would reemphasize that there is evidence that it exists in the rat, dog, rabbit and man (1). The deductions of Hardy and DuBois, as well as Burton's observation, seem to support the hypothesis that man may show nonshivering thermogenesis. The critical point concerns interaction of the two systems—shivering and nonshivering.

Dr. Fremont-Smith: I have tried to look at the organism as a dynamic, homeostatic creature, responding to a new environment while in the process of growth and development. On such a basis we cannot expect a single given stimulus to produce a characteristic response. In fact, if the conditions are varied even to a small degree, a diametrically opposite result might occur from a given stimulus. Thus we must know not only the conditions under which the organism is maintained during any given experiment, but the previous history as well. We are far too casual in our use of the concept of control. Control with respect to what? The controls are different in different experiments done by the same investigator; and the controls vary so widely from one laboratory to another that it is a wonder any results agree at all. If work is to be confirmed, it must be repeated in the most exacting details in control as well as experimental procedure.

Dr. Hart has brought out the importance of considering the animal in a more normal environment than that of a small cage in an artificially controlled temperature before making any generalizations about acclimatization. Conrad Lorenz in the School of Ecology has a great deal to offer us in the solution of this problem.

Likewise, more comparisons should be made with results from hibernation and high-altitude studies, as these offer similarities and differences that might give valuable clues to the solution of the problem of acclimatization. Thus for example, overventilation is a behavior pattern that is characteristic of the early stages of cold exposure as well as of high altitude.

Another area of investigation relating to adaptive behavior is a relatively unexplored but fertile field, the effects of induced fever. A small lowering of environmental temperature in a febrile animal will result in violent shivering such as is only obtained in a control animal by drastic temperature changes.

Dr. Merva Cottle: Do we have any data on the tissues of the cold-acclimatized animal, particularly on the muscle tissue? Is there an increased sensitivity to noradrenaline in the muscle tissues studied by Dr. Depocas? The effects of noradrenaline and the thyroid hormones have been determined on *in vitro* tissues of nonacclimated animals. The levels of the catecholamines in the cellular membrane and cells and in urine should be of significance in the cold-acclimated animal; possibly

the A-V difference would give us some idea of the utilization of noradrenaline in the animal responding to cold.

DR. KNIGGE: Throughout the section on the endocrine glands, particularly in the papers and comments of Dr. D'Angelo and Dr. Cottle on the thyroid, the question of techniques was raised repeatedly and I would like to comment on this. I would like to mention some experiments we have done with the hamster which illustrate how deceptive some techniques and the interpretation of certain parameters of thyroid function can be. When the hamster is chronically exposed to cold the thyroid undergoes some remarkable histological changes; these include a decrease in cell height, a marked enlargement of the follicle and storage of colloid. These changes are the classical histological features that are interpreted as hypofunction and involution. Examination of the gland by a gamut of metabolic studies, however, leads to the inescapable conclusion that the thyroid is actually secreting increased amounts of hormone. The explanation appears to be that the hamster thyroid, at least under conditions of cold exposure, is capable of both storage and secretion of increased amounts of hormone. With respect to Dr. Des Marais' question as to the value of the rate of release as a measure of what the gland is secreting, it should be pointed out that a measure of the iodine content of the gland must be used in conjunction with the release rate in order to arrive at some estimate of the daily hormone output. In view of the recent demonstration that iodinated proteins other than thyroxin and triiodothyronine may leave the gland, validity of rate of release of thyroidal I^{131} as an index of hormone secretion should be carefully evaluated. Another very interesting result from Dr. Heroux and Dr. Schönbaum's paper was the data from one of their groups of cold-exposed rats showing evidence of increased adrenal size, increased number of fasciculata cells together with a subnormal rate of *in vitro* steroidogenesis. I wounder if this could mean that there may be other trophic hormones concerned in this process. We have not considered, for example, growth hormone or the gonadatrophins, which may be very important in this respect. Another possible explanation for these divergent results is that the *in vitro* measurement of steroidogenesis may not be applicable under these particular experimental conditions. The validity of the *in vitro* method for assay of ACTH has been fairly well established, but it does not follow that the *in vitro* performance of adrenals from all experimental animals accurately reflects their actual *in vivo* rate of hormone delivery. Chromatographic separation of the ultraviolet absorbing material from these incubates would have been an additional simple step which could yield more information about steroidogenesis of the individual hormones. In response to Dr. Schönbaum's question on other techniques, extremely sensitive fluorometric procedures are now available for the measurement of the steroid content in both the adrenal and in peripheral blood. The content of compound B or F in the gland appears to be a sensitive index of the action of ACTH at the adrenal.

DR. HEROUX: I would like to reply to Dr. Knigge's comment concerning hypertrophy of the adrenal in the cold-acclimated rats and its reduced activity. If you look at this graph (fig. 1) you will see that in rats kept at 6°C for 12 weeks, the adrenal gland hypertrophies during the 1st week and then remains at the same weight for the rest of the cold exposure. However, if the adrenal activity is measured, it increases for 2 or 3 weeks and then decreases at a new level well above normal. It can be seen that the activity does not parallel the increase in weight. I am therefore inclined to think that Dr. Knigge is right when he says that there may exist an adrenal weight factor in the pituitary different from the ACTH factor. There is some evidence in the literature for the existence of this adrenal weight factor (2–4).

DR. KELLER: Is adrenal hypertrophy always associated with increased activity?

DR. HEROUX: In the outdoor rats, as I mentioned before, there is no adrenal hypertrophy and yet the *in vitro* method shows an increased secretion.

DR. KELLER: You mean there is none compared with adrenal weights encountered in laboratory experiments?

DR. HEROUX: No, none comparable to that in the outdoor summer controls; if you compare the weights of the adrenals of summer and winter rats, there is no difference, but the *in vitro* secretion is higher in the winter rats.

DR. KELLER: The reason I ask this question is because so much emphasis has always been assigned to adrenal weights. Through the years an increase in weight has been interpreted as specific evidence of increased activity; but is a failure to increase in weight indicative of an adrenocortical inadequacy or hypofunction?

DR. HEROUX: I think that the increase in weight of the adrenals, or of any other gland for that matter, means nothing as far as the hormonal output of that gland is concerned. Since there are so many elegant direct methods for measuring the rate of hormone production in a gland, it is unbelievable that workers should still use gland weight as an index of activity.

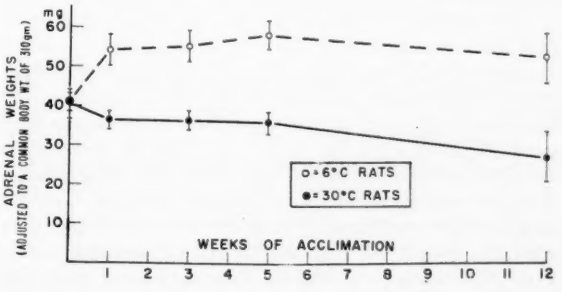


FIG. 1

I would like to take this opportunity to mention the reasons why we undertook this comparative work on outdoor and indoor rats. When we began work on the indoor cold acclimation problem, we were aware that the experimental conditions in the laboratory were far from natural. We kept each rat in an individual cage with no protection at all and exposed it to a continuous and constant cold temperature 24 hours a day with regular 8-hour periods of light per day. No such conditions exist in nature, of course. So we wondered how many of the changes that we had observed in these indoor rats were essential to increased cold resistance. Due to the continuous cold stimulus, some of these changes might be superimposed on the essential adjustments for cold adaptation. If it was possible to develop under more natural fluctuating environmental conditions the same degree of cold resistance observed in rats continuously kept in a cold room, it would be possible to differentiate between essential and nonessential adjustments.

Under proper experimental conditions, we found that many of the changes observed in the indoor cold-acclimated rats can be dispensed with and yet the same degree of cold resistance can be developed. The most important changes that do not show up in the outdoor winter rats are the thyroid hyperactivity, the peripheral vasodilation, the peripheral cold injuries, the general hypertrophy of the visceral organs including the adrenal glands, and cardiovascular lesions (5, 6).

DR. SCHÖNBAUM: I should like to respond very briefly to Dr. Knigge's remarks. I am aware of the omission of chromatographic data in my paper. We did, in fact, chromatograph our incubation media, but we never observed any major component other than that with characteristics similar to corticosterone. However, I did not feel that our chromatographic studies were sufficiently refined and sensitive to warrant extensive discussion. For example, we never observed the steroids described by Birmingham and Kurlentz (7).

It is important to be aware of one's own limitations when working in a relatively small unit and I feel that it is better not to attempt too much. This would be my answer to the remarks of Dr. Pace and some others. I am not aware of any very convincing report that there are conditions under which another steroid replaces corticosterone as the major steroid secreted in the rat.

The discrepancy between reduced steroid output *in vitro* and increased size of the adrenal glands and the number of adrenocortical cells is another matter. While technical considerations can by no means be excluded, there are a number of important biological factors that merit thought. Changes in the structure of the adrenocortical cells may well be responsible for these effects. Adrenal cells in rats exposed to cold for many months might differ from those of rats very recently exposed to cold. Dr. Sellers, who studied the appearance of adrenals from rats exposed to cold for long periods of time, felt that there were some structural changes (personal communication). The changes could affect the rate of formation of steroids *in vitro*.

I have a final remark about the adrenal ascorbic acid. Inside the adrenal cells the concentration of ascorbic acid is ten times that in the surrounding plasma. Considering the diffusibility of ascorbic acid, some specific mechanism must be required to maintain this concentration gradient. Under the influence of ACTH this mechanism might be affected, permitting ascorbic acid to leak out; it seems to be very sensitive to the blood level of ACTH. This, however, does not imply that there is a direct relationship between this process and the effect of ACTH on the synthesis of steroids. Probably there is always enough ascorbic acid available to supply the demands for it made by the adrenal cortical cells. See also (8).

MRS. HOIJER: There is indeed a high concentration of ascorbic acid within the cells of the adrenals as measured by Dr. Dugal. Stimulation by cold as well as exogenous ACTH results in increased outflow from the glands. In the experimental work of Dr. Slusher the differences between the amount of outflow and the initial concentration in the adrenals indicated a metabolic utilization of ascorbic acid within the tissues of the adrenal glands. The role of ascorbic acid in steroid synthesis has been discussed earlier in this Symposium.

DR. D'ANGELO: Two generalizations strike me about this conference on cold; first, it has exposed so many areas of deficiency in our information that no single person, however dedicated to his own area of specialization, can listen and not feel some humility about the subject; secondly, some comment might be made with respect to the senior scientists' admonition to their younger colleagues working in this field. Perhaps the admonition should be more in the nature of a suggestion that the results of their experiments should be placed in broad perspective. Physical limitations are such that no one can possibly have a complete understanding of all facets of the problem of cold acclimation and still explore deeply his own studies. What one must do, I suppose, is to come to meetings like these and listen, no matter how difficult it may be at times. Certainly, there can be few of us here who have not gained one or two ideas with which to pursue his experimental ramifications.

With respect to some specifics deriving from the conference, one might remark about the fact that the two important integrative systems (nervous and endocrine) in the body are themselves remarkably integrated in cold acclimation, probably more so than in any other environmental condition. Some very broad biological problems were touched upon, perhaps too lightly; we have been considering survival as the major criterion for successful acclimation to cold. No one seems to have mentioned anything about the ability of the species to reproduce in a cold environment. Much attention was given to the possible importance of ascorbic acid in cold

acclimation. Dr. Booker was intrigued by the rapidity of change in adrenal ascorbic acid as a reflection of pituitary ACTH function in acute stress. Dr. Hoijer indicated the three avenues (chemical manipulation of phenylalanine to catecholamines, hydroxylation of steroid precursors to cortical hormones, and participation in the electron transport system) by which ascorbic acid may act. It is of interest that the highest concentrations of ascorbic acid in the body are found in some members of the endocrine system; namely, adrenal, hypophysis and ovary. With the exception of the adrenal, ascorbic acid content of these other organs has rarely been measured in the cold-exposed animal. Also, the critical roles of both adrenal medulla and cortex in cold acclimation give no significant clue as to why these separate endocrine glands have topographically merged in the course of evolution. Another problem brought into clearer focus in this conference concerns the apparently great differences even among closely related species as to the endocrine interplay. Insofar as endocrine interaction is concerned, it seems that each species achieves successful hormonal balance in the cold via similar basic mechanisms, operating, however, at vastly different intensities. In the hamster, the role of the adrenal cortex appears to be less critical than in the guinea pig, at least in chronic exposure. In the rat, adrenal function may wax and wane during cold stress. It would be a harrowing choice, indeed, for any animal if it had to take with it only one endocrine gland to a cold environment. Some might prefer the thyroid to the adrenal or vice versa; certainly neither would function well without the adenohypophysis, and here, too, direct anatomic continuity with the hypothalamus might be essential.

DR. FLETCHER: At this stage of this extremely interesting meeting, when all the experimental results have been described in full and we have nearly finished our discussions, thoughts are beginning to turn to the next meeting in a few years' time, and it seems to me well worthwhile spending just a little time on talking about future experiments. We have about eight days left before we shall all move back to our laboratories, where we shall take up our research again and study all sorts of biological systems under widely varied temperature conditions. There are two alternatives: one is that we could all work individually, without reference to other work that is going on, so far as these thermal conditions are concerned; the other alternative means acceptance of discipline, if a lead could be given. So I am suggesting that it might be possible and useful for a lead to be given in recommending standardization. It might well be that more uniformity and more meaning in our results will come from concentrating our efforts on a smaller range of exposures in terms of temperature and time, in concentrating on a reduced number of species for a short time, and in thinking of the important variables which can be controlled. When we come to draw an analogy with the field of heat acclimatization which was mentioned earlier by Dr. Adolph, we can see the possible benefits. That field developed rather slowly and perhaps not as efficiently as it might have because of the widely varying conditions of temperature exposure and time exposure. If we could concentrate on the rat as a small animal with an exposure reference time of a determined number of minutes within a fixed temperature range, we might improve our results. In the field of human physiology we might prefer to work on adult males in the range of 18 to 25 for reference purposes, and we should also have them at a fixed reference temperature for an hour before experiments. I would like to suggest that standardization of conditions of experimental work be considered at this meeting.

DR. MASORO: Several speakers have been referring to those of us who work in the field of intermediary metabolism as 'the biochemists.' Everyone should recognize that we are all physiologists and that we are all trying to solve the same physiological problem, namely, the mechanisms by which the mammal acclimates to low environmental temperatures. It is true that at present it is difficult to relate the work done at the molecular level to cold acclimation as seen in the intact animal. However, I should like to remind those fellow physiologists who work in other areas of physiology that studies at the intermediary metabolic level in the field of cold acclimation have been undertaken only in the last few years. If physiologists in general have a bit of patience, they will see great gains in our understanding of cold acclimation from the data obtained at the molecular level of investigation.

REFERENCES

1. CARLSON, L. D. (This Symposium) *Fed. Proc.* 19, Suppl. 5: 25, 1960.
2. LI, C. H., F. S. GREENSPAN, M. E. SIMPSON AND H. M. EVANS. *Hormone Assay*, edited by C. W. EMMENS. New York: Acad. Press, 1950, p. 812.
3. DIXON, H. B. F., M. P. STACK-DUNNE AND F. C. YOUNG. *Nature, London* 168: 1084, 1951.
4. REINHARDT, W. O. AND C. H. LI. *Proc. Soc. Exper. Biol. & Med.* 77: 229, 1951.
5. HEROUX, O., F. DEPOCAS AND J. S. HART. *Canad. J. Biochem. & Physiol.* 37: 473, 1959.
6. HEROUX, O. *Canad. J. Biochem. & Physiol.* 37: 1247, 1959.
7. BIRMINGHAM M. K. AND E. KURLENTS. *Canad. J. Biochem. & Physiol.* 37:510, 1959.
8. STAUDINGER, H. Proc. 4th Internat. Congress Biochem., Vienna, 1958 (1959), p. 74.

Summary of the Symposium[1]

DOROTHY JARED HOIJER AND ROBERT E. SMITH
Department of Physiology, University of California School of Medicine, Los Angeles, California

DURING THE THREE DAYS AT THIS SYMPOSIUM we have heard a great deal about man and the rat in the cold. The responses of the total animal to cold can be measured only by such limited means as body temperature, oxygen uptake and excretion analyses. These gross techniques fail to give us an adequate understanding of the complex processes that contribute to the heat production necessary for survival under lowered environmental conditions. Consequently we have turned to the rat as one means of investigating many of the changes that occur during acclimation to cold. Acclimation under the controlled conditions of the laboratory can be quite different from acclimatization in the natural environment, with its seasonal changes and variations in diet; however, it is in the laboratory that most of the metabolic studies have been done.

The thermogenesis of acclimation differs from that of short-term cold exposure in that shivering decreases and chemical heat production takes its place. Since the muscle bed is the source of heat production in shivering, it is logical that it can be the source of a large part of the heat produced by chemical means. Curarized, cold-acclimated animals do maintain their body temperatures more effectively than do the control animals. The heat production of the muscle bed is particularly sensitive to noradrenaline, as measured by oxygen uptake following infusion of this hormone. The shift from shivering to nonshivering thermogenesis apparently coincides with a shift in the muscle innervation from somatic to sympathetic nerve stimulation, or at least from a cholinergic to an adrenergic mediation. Despite the disproportion between muscle and liver mass, the latter, as a most active metabolic tissue of the body, has been used extensively for the study of mechanisms of cold adaptation. The relative thermogenic importance of liver in cold acclimation remains uncertain.

The time necessary for acclimation to occur varies from 1 to 2 or more weeks, when metabolic activity reaches a peak and then declines to a plateau well above normal for the duration of exposure to cold. Among the most easily measured metabolic parameters of the cold acclimated state are oxygen consumption and the exchanges of glucose, protein and lipid. These functions are mediated through activation of neural processes. Cold stimulates hypothalamic thermosensitive elements which respond directly to topical changes in temperature. While in man, and probably to a varying extent in other mammals, receptors of the skin mediate conscious sensations of temperature through thalamocortical pathways, the major control of body temperature remains at the hypothalamic level.

The adrenal medulla is a homologue of the postganglionic sympathetic outflow and responds to hypothalamic neural stimulation by an immediate discharge of stored catecholamines. This rapid response to changed environmental conditions or imbalance of homeostatic conditions, such as hypoglycemia, is of utmost importance to survival in the cold.

Hypothalamus likewise activates the pituitary gland, by mechanisms involving both neuronal control and a humoral feed-back regulation entailing both intrinsic and extrinsic hormonal mediation. The resulting outputs of TSH and ACTH assure an adequate production and delivery of thyroid and adrenocortical hormones necessary for the increased metabolism of the cold-exposed animal.

Thyroidectomized, or thiouracil-treated rats survive only a few days in the cold, but if the surgery or treatment is performed after acclimation has occurred, the animals are able to survive much longer than the nonacclimated controls. Thyroid hormone is essential to a readjustment of mechanisms necessary to meet the need of reduced thermal conditions. Comparative studies of enzyme systems and other cellular preparations of cold, thyroxine-treated and normal animals show an increased stimulation in cold-and-thyroxine-treated animals. However, the results indicate that the various functions measured are not equally dependent upon thyroxine mediation in the cold.

During the early phases of cold acclimation, *in vitro* measurements show a heightened production of the corticosteroid hormones. *In vivo* differences between the production of hormones by normal and cold-acclimated animals is difficult to assess because of destruction by the liver, particularly with the increased reduction of the steroids under the influence of thyroid activity.

Hormonal balances are closely linked to the concen-

[1] This summary was written on the basis of material presented during the current Symposium. It is, therefore, not intended as a review of the literature pertaining to cold acclimation.

trations of several factors such as supply of precursors and activators of the processes of synthesis. Ascorbic acid is a necessary element for the maintenance of adequate levels of catecholamines and the corticosteroids and may accelerate the transfer of electrons in the particulate fractions of the cells to increase the oxidation of substrate necessary for energy requirements. The concentration of this vitamin is markedly increased in the cold, particularly in the adrenals, kidneys and brown fat. If the animal cannot synthesize the ascorbic acid, it retains a greater than normal amount from exogenous sources. The precursors of the medullary and thyroid hormones can be obtained from proteins, while the basic units for the corticosteroids are the acetates from lipid degradation.

The active form of the acetate, acetyl CoA, is a basic interchangeable unit in the synthesis and degradation of almost all of the metabolic processes. It has been used to delineate the mechanism of degradation and synthesis of glycogen, glucose and the lipids. It has been observed that cold-acclimated animals can maintain their glycogen stores under the additional stress of fasting much better than the control animals. Despite this maintenance of the glycogen stores, turnover rates of glucose and glycogen and the production of CO_2 and H_2O are increased in the cold-acclimated animals.

Acceleration of these metabolic pathways involves an increase in the activity and concentration of at least some of the many enzymes of the systems involved, probably those that are rate-limiting. This is indeed true of the muscle glucokinase and glucose-6-phosphatase which are reportedly increased in cold-acclimated animals. Changes in activity of glucose-6-phosphatase are also associated with increased thyroid activity, but further study is indicated. The liver tissues of cold-acclimated animals also show an increased hexokinase activity and a 50% increase in the rate of pyruvate formation from phosphoglycerate. Additional experiments have demonstrated the increased rate of oxidation of the components of the Krebs' cycle in cold-acclimated animals, with increased activities of succinic and malic dehydrogenases, and likewise lactic dehydrogenase.

During the initial 30-minute period following glucose C^{14} injection into cold-acclimated and control animals, more glucose is metabolized to CO_2 and H_2O in the cold animals than in the controls. After a period of 2.5 hours, however, the cold animals oxidize less than the warm acclimated rats. This is in agreement with the earlier work on the increased conversion of C^{14} to glycogen in cold rats to maintain adequate levels of this possible substrate. The higher total production of CO_2 in cold-acclimated animals must, therefore, come from other sources than glucose, such as the proteins and lipids.

The protein turnover rates are more rapid in animals subjected to cold, and the total mass of circulating proteins of the plasma is increased. The latter may be due, in part, to the hemoconcentration that occurs in cold. The platelet count is high in the initial period of cold exposure and falls to normal within a short period of time; the fibrinogen rises more slowly, but also returns to normal. The active antibody formation, however, is lower in cold animals.

The high turnover rates of protein, increased nonprotein secretion in the urine, and low weight gains of growing animals, indicate a reduced anabolism and increased catabolism of proteins in cold-acclimated animals. The corticosteroid effect of increasing transamination and deamination reactions would favor the conversion of exogenous supplies of protein to the carboxylic acid counterparts that can be used as substrates for oxidation under the stress of cold.

Controlled diet studies have shown that protein is not the preferential food, but that a high-fat diet is more suitable for survival in the cold. Early studies of cold acclimation demonstrated that cold itself is a lipotropic agent and can prevent the deposition of fat in the liver of animals given a high-fat diet. The liver tissues of cold-acclimated animals are able to oxidize the long-chain fatty acids more rapidly than are the controls, and they also have a reduced ability to synthesize the lipids from acetate-1-C^{14}. This is not because of a deficiency of glycerol, since this can be obtained from the adequate glycogen stores. The increased oxidation of lipids, rather than synthesis, is stimulated by the increased levels of CoA found in the tissues of cold-acclimated animals, as well as by other factors not yet determined. The increased oxidation of lipids is facilitated by the noradrenaline-stimulated mobilization of fatty acids from the adipose tissues. This effect of adrenaline, and particularly noradrenaline, has been demonstrated repeatedly by infusion experiments and *in vitro* liver slice studies.

The lean condition of animals maintained in the cold can be attributed to increased turnover rates and oxidation of glucose, proteins and the lipids, and to a change in the water and electrolyte balances. As noted earlier, exposure to cold produces a decrease in plasma volume and an increase in hemoconcentration. Changes in electrolytes include increases in sodium and potassium concentrations and a decrease in tissue chlorides during the early stages of cold exposure with a return to normal levels after a period of time. Magnesium concentrations, however, increase and continue to remain high in cold-acclimated animals. The effect of the increased hormonal output induced by cold exposure on the electrolyte changes has not been determined.

The importance of the hormones in acclimation to cold has been demonstrated in the ability of animals of different age groups to survive. Too young an animal has not developed a sufficiently balanced hormonal system to withstand acute stress, and when age causes a decreased hormonal function, the metabolic processes dependent upon such stimulation cannot be accelerated sufficiently to combat the lowered environmental conditions. An animal subjected to the stress of cold must increase its enzyme concentrations and activities suffi-

ciently to handle the greater turnover of substrate in the various metabolic processes of oxidation, decarboxylation, transamination, deamination, phosphorylation, dephosphorylation and the other countless enzyme-controlled processes of the body.

A closely controlled relationship of oxidation of substrate, phosphorylation and conversion of energy to heat is found in the subcellular elements of the tissue. The mitochondrial and extramitochondrial particles control the ratio of phosphorylation to oxidation, and this ratio is evidently lower in the cold-acclimated animal than in the control. While increased oxidation is necessary for increased heat production, this may not imply a concurrent requirement that correspondingly more chemical energy be bound in high-energy phosphates; this is particularly true in a system of reduced anabolism. These complex enzymatic processes of phosphorylation and dephosphorylation involve a large percentage of the metabolic functions of the mammalian system.

Adaptation to cold requires the establishment of a new steady state, capable of increased heat production within the framework of a metabolically balanced system. We see the accomplishment of this delicate adjustment in the acclimated animal, or in man, living comfortably under conditions that could be critical to a nonacclimated subject.

Whether working from the whole animal to the *in vitro* subcellular level, or from the particulate fraction to the whole animal, the information acquired must be meaningfully integrated to the one concept of the maintenance of homeostasis under lowered environmental temperatures.

Concluding address[1]

REAR ADMIRAL RODOLFO N. PANZARINI
Instituto Antártico Argentino, Buenos Aires, Argentina

THE INTERNATIONAL SYMPOSIUM ON COLD ACCLIMATION has been accomplished with a success commensurate with the high scientific quality of those that have contributed to its materialization. Coming from different countries the participants have given commendable proof of the advances achieved in their respective homelands in the academic and applied aspects of man's behavior in an environment of low temperature.

In getting together to explain and compare the results of your experiments, your studies and reflections, and to share your experiences, both successful and otherwise, you have again made manifest the abiding conviction of the scientist that the foundation of our civilization rests ultimately upon the collaborative efforts of the men of all races and tongues for the satisfaction of that common desire to reduce the boundaries of our ignorance. Of the determination of that desire, of how exceptional is the nature of human ingenuity and of how unlimited its possibilities, the subject matter of this Symposium is a very typical example. Thus a physical characteristic, cold, though itself largely unfavorable to life, is in fact being studied not only to improve our protection against its harmful effects, but also to profit from the good it might enclose. Within those activities of man that are to make him ascend from the surface of the earth, go towards the higher latitudes, or artificially create frigid environments, are the many possibilities for practical application of what is certainly to become known regarding the peculiarities of the human reactions to enveloping cold. Your work, gentlemen, is therefore one that gives comfort to the spirit in satisfying that mysterious urge of man to investigate everything, and one that also touches the heart because it feeds the confidence of those that hope and need.

For the Argentine Antarctic Institute, to participate in the sponsorship of this International Symposium on Cold Acclimation has been a great privilege, and to welcome such a qualified group of investigators to meet within its premises has been a special honor and a pleasure.

On my own behalf and that of my staff I thank you all for the distinction thus bestowed upon our Institute, and may I ask you to join me in a toast to the success and continutity of international cooperation in scientific research, and to your personal happiness.

[1] Delivered at the dinner in honor of the participants of the International Symposium on Cold Acclimation on Friday, August 7, 1959, at the Alvear Palace Hotel, Buenos Aires, Argentina.

XUM

Biology Library

December 1960 · VOL. 19 · NO. 4 ·

PUBLISHED IN THREE PARTS

PART III

Supplement no. 6

LIBRARY

Federation Proceedings

Biology Library

An Annotated Bibliography

LABORATORY ANIMALS

Published quarterly by the
FEDERATION *of* AMERICAN SOCIETIES
for EXPERIMENTAL BIOLOGY

FEDERATION PROCEEDINGS DECEMBER 1960

Supplement No. 6

A GUIDE TO PRODUCTION, CARE AND USE OF

LABORATORY ANIMALS

An Annotated Bibliography

JULES S. CASS, M.SC., D.V.M.

IRENE R. CAMPBELL, A.B. LILLI LANGE, Cand. phil., Chem.

The Kettering Laboratory
in the Department of Preventive Medicine and Industrial Health,
College of Medicine, University of Cincinnati, Cincinnati, Ohio

Published by

FEDERATION of AMERICAN SOCIETIES for EXPERIMENTAL BIOLOGY

XUM

© *Copyright 1960 by*

FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY

The preparation and publication of this annotated bibliography
was supported by Research Grant RG-6113(C1) from
the National Institutes of Health

PRINTED IN THE UNITED STATES OF AMERICA
BY WAVERLY PRESS, INC., BALTIMORE, MARYLAND

Introduction

Knowledge is of two kinds: we know a subject ourselves, or we know where we can find information upon it.

Boswell's *Life of Johnson*, I: 558

THIS GUIDE was prepared in an attempt to meet the need of locating sources of information and techniques as an aid in resolving some of the more common problems in the production and use of laboratory animals. Facts concerning the usual species of these animals are scattered widely and often hidden in the literature.

Many investigators may possess in their files specialized data more extensive than those in this compilation. However, practical information concerning laboratory animals is difficult to locate and frequently its existence is unknown to the people working with them. In many instances, the title of an article in no way discloses that it contains normal physiologic data, or a new technique and piece of equipment applied in the use of animals. Because of this, much time and funds have been and are being spent in a duplication of effort.

This bibliography grew through the years, in the private collection of references of the principal author, and in the files of the library of The Kettering Laboratory, as tasks performed with animals required various information. A continuing selection and the annotation of references from the earlier and current literature were initiated systematically in 1959, supported by grants from the U. S. Public Health Service, to make available the compilation of references, equipped with detailed author and subject indexes.

USES AND USERS

This bibliography should permit a user to locate principal sources of information that deal with the procurement, production, care and use of laboratory animals. This information may be found useful:

1) In the design and construction of facilities and equipment for housing, transportation, and care of animals.
2) To guide a worker employing animals to published physiological data and techniques for specific applications.
3) As biological bases (intrinsic and extrinsic) for the selection of experimental animals, and for the sound design of experiments using animals.
4) As a guide to the significance of environmental factors when interpreting the results of investigations using animals.
5) In the preparation of training courses for people working with laboratory animals at various levels of responsibility.

The following groups of individuals should find helpful sources of information in this compilation: 1) investigators in the fields of biological and medical diagnosis, research and development; 2) administrators of organizations using laboratory animals; 3) producers and caretakers of laboratory animals; 4) individuals concerned with the biological testing of biological products, and the biological assaying of chemicals and drugs; 5) animal and laboratory technicians; 6) veterinarians; and 7) teachers of laboratory courses in biology.

COVERAGE AND ARRANGEMENT OF MATERIAL

For the present compilation, the more basic treatises and articles contained in the earlier files have been consulted in the original and annotated. Greater emphasis has been placed, however, on the inclusion of the more recent publications as they are noted in the course of routine scanning of periodicals and other material received in the library of The Kettering Laboratory.[1] Articles of interest appearing in the literature not received in the library are obtained wherever possible in the form of reprints and photocopies.

The references, by the interpretation of the major interest of their contents, have been distributed into the following sections:

Section 1 deals with the normal morphologic and metabolic aspects of anatomy, physiology, and psychology, including the role of factors in the environment.

Section 2 covers the various causative agents, the natural history, the pathogenesis, as well as the diagnosis, prevention, control, eradication, and treatment of spontaneous diseases.

Section 3 is concerned with nutritional matters including food and water requirements, special diets and antibiotic and hormonal additives in the diet.

Section 4 deals with the practical aspects of the operation of colonies for the production of laboratory animals.

Section 5 includes consideration of the surroundings into which animals are placed and in which they are maintained. This includes the buildings, their design and construction; various kinds of equipment for caging, watering, feeding, and disposal;

[1] In addition to the titles listed in Section 9, somewhat over one hundred titles, including *Index Medicus* and *Chemical Abstracts*.

XUM

supplies and sanitary maintenance; and equipment to control the environment and its maintenance.

Section 6 contains references with information on the procurement of animals, matters concerned with transportation, practices of quarantine (including the identification and marking of animals), as well as laws and standard guides relating to the use of laboratory animals.

Section 7 is concerned with the various methods of handling, holding, and exposing animals; clinical, laboratory, and surgical techniques including the use of anesthesia, resuscitation, and euthanasia.

Section 8 includes the planning, cost accounting, personnel management and training, record keeping, and public relations aspects involved in the administration of colonies of laboratory animals.

Section 9 includes abstract journals that have been found especially useful as sources of information as well as periodical publications dealing with the procurement, production, care and use of laboratory animals.

Abstracts of articles deemed important, and which could not be seen in the original, are used occasionally and the source of the abstract is cited.

The references on diseases are limited to those that occur spontaneously and exist peculiarly in breeding colonies and in the environment of the laboratory. References concerning spontaneous diseases, experimentally induced, were included to provide information on the natural history of these diseases, means for their control and treatment, and the techniques involved. In some cases, articles concerned with pathologic responses were selected because they contained normal physiologic measurements as well as new methods for these measurements.

The literature on the more practical aspects of the production and maintenance of laboratory animals is comparatively recent. A particular effort has been made to include as much information as possible on these subjects.

While the cross-references indicated at the end of each section permit the user of the guide to consult related abstracts given in other sections, a detailed and descriptive subject index was considered most essential in the location of the specific information. Without such an index, specific details would otherwise be buried, so that the principal purpose of the bibliography would not be achieved. Information concerned with the more commonly used small mammals are indexed rather extensively. Other animals, such as farm, captive wild animals, fish, amphibia, invertebrates, etc., are indexed more generally, and mainly because they are noted occasionally in the contents of abstracts, or because information contained is concerned with their production and use in the laboratory.

Throughout, the selection of articles is being directed expressly to supplement and expand, but to avoid duplication of other bibliographies of an extensive nature.

From the subject index, it has become evident that certain categories of information are less adequately represented than others. It is planned, in a supplementary compilation, to intensify the search for references in these categories.

Suggestions for the inclusion of material, as well as advice as to any errors in the present bibliography will be welcomed, so that it may become a truly useful tool in locating information concerning the production, maintenance and use of laboratory animals.

Contents

INTRODUCTION iii

1. NORMAL ANATOMY, PHYSIOLOGY, PSYCHOLOGY, including the Role of Factors in the Environment 1

2. DISEASES, ABNORMALITIES, INJURIES, including Diagnostic Tests, Prevention, Eradication, Control, Treatment 45

3. NUTRITION: FOOD AND WATER REQUIREMENTS; DIETS; DIETARY SUPPLEMENTS OR ADDITIVES 79

4. BREEDING PROGRAMS: DESIGN AND OPERATION OF PRODUCTION COLONY ... 88

5. DESIGN AND OPERATION OF MAINTENANCE AND USE COLONY 99

6. PROCUREMENT AND USE OF ANIMALS, including Marking of Animals, Standards, Legislation, Transportation, Quarantine 110

7. SPECIAL TECHNIQUES; PREPARATION OF ANIMALS FOR USE; HANDLING; ANESTHESIA; EUTHANASIA 116

8. ADMINISTRATION OF COLONIES: RECORDS, COSTS, PERSONNEL, PUBLIC RELATIONS 133

9. PERIODICAL AND OTHER PUBLICATIONS OF GENERAL INTEREST 135

AUTHOR INDEX 137

SUBJECT INDEX 145

Acknowledgments

THE ENCOURAGEMENT to prepare and publish this first compilation came from many individuals, Dr. R. A. Kehoe, Director of The Kettering Laboratory; Dr. T. Ruch, University of Washington, Seattle; Dr. W. H. Eyestone, National Institutes of Health, Bethesda, Maryland; Dr. D. Jenkins, Fort Detrick, Maryland; Mr. B. Hill, Institute of Laboratory Animal Resources, National Research Council, Washington, D. C.; Dr. E. C. Chamberlayne, Pan American Sanitary Bureau, World Health Organization, Washington, D. C.; Dr. G. E. Jay, Jr., National Institutes of Health, Bethesda, Maryland; Dr. J. Lieberman, U.S. Public Health Service, Communicable Disease Center, Atlanta, Georgia; Dr. L. H. Schmidt, Institute of Medical Research, Christ Hospital, Cincinnati, Ohio; officers and directors of the Animal Care Panel, Argonne, Illinois. Their suggestions, and criticisms are gratefully acknowledged. Mrs. E. Cumming, New City, Rockland County, New York, on several occasions graciously provided lists of useful references from her private collection. Greatly appreciated is the assistance and cooperation of the staff of the Division of Bibliographic Research, particularly Arlene Mandell who has done most of the typing, Evelyn Widner and Irene P. Kukainis who have helped with the details of the final preparation of the manuscript as the need arose.

1. Normal Anatomy, Physiology, Psychology[1]

Including the Role of Factors in the Environment

1. WADA, T. *Anatomical and Physiological Studies on the Growth of the Inner Ear of the Albino Rat.* (*Am. Anat. Memoirs* No. 10) Philadelphia, Wistar Institute of Anatomy and Biology, 1923, 174 pp.

2. DONALDSON, H. H., ed., *The Rat. Data and Reference Tables for the Albino Rat* (Mus norvegicus albinus) *and the Norway Rat* (Mus norvegicus). 2nd ed. (*Memoirs*) Philadelphia, Wistar Institute of Anatomy and Biology, 1924, 469 pp.

Biology, genetics, anatomy, physiology, pathology and growth are discussed.

3. HERRICK, C. J. *Neurological Foundations of Animal Behavior.* New York, Holt, 1924, 334 pp.

The book contains the following chapters: Analysis of behavior; receptive apparatus; vital energies; excitation-conduction gradients of protozoa; precursors and the dawn of the nervous system; tissue differentiation in the nervous system; nervous system of worms, insects, vertebrates, dogfish; reflex patterns in fish; evolution and functional factors of the forebrain; mechanism of correlation, integration and dominance; apparatus of modifiable behavior; fixed and modifiable behavior.

4. HAMMOND, J. AND MARSHALL, F. H. A. *Reproduction in the Rabbit.* London, Oliver, 1925, 235 pp.

5. SIMMONDS, J. P. The blood of normal mice. *Anat. Record* 30: 99–106 (May), 1925.

Differential counts in a series of mice (strain not given) gave the following results (%): lymphocytes 50–65, polymorphonuclears 24–50, eosinophils 0.5–3, large mononuclears 3–10, basophils less than 1. The percentages of the 5 different types of leukocytes ranged as follows (%): unbroken ring 2–4, broken ring 18–22, segmenting ring 10–26, knot- or loop-shaped 46–60, multilobular 4–8. The corresponding percentages for these 5 types of leukocytes in the bone marrow were, respectively: 46.7; 10.0; 5.3; 34.7; 3.3.

6. SUNDSTROEM, E. S. The physiological effects of tropical climate. *Physiol. Revs.* 7: 320–62 (Apr.), 1927.

The following physiological effects of tropical heat, light and humidity are covered by this review (194 references): body and skin temperature, heat loss, basal metabolism, blood distribution, water regulation, urinary excretion, acid-base equilibrium, non-protein N, P and lipoid constituents in the blood, suspension stability and number of red blood cells, pulse and respiration rate, growth, reproduction, hair, nails, pigmentation, endocrinal functions, and nervous system.

7. KING, H. D. AND DONALDSON, H. H. *Life Processes and Size of the Body and Organs of the Gray Norway Rat During Ten Generations in Captivity.* Philadelphia, Wistar Institute of Anatomy and Biology, 1929, 106 pp.

After 10 generations in captivity the captive gray Norway rat differs from the wild type as follows: increase in the rate of body weight to body length and in the weight of the hypophysis, decrease in weight of brain, thyroid, suprarenals (especially female suprarenals). Comparison of the captive gray and the albino leads to the conclusion that 10 generations of captivity have not given the captive gray the organic constitution of the albino.

8. PEARCE, L. AND CASEY, A. E. Studies in the blood cytology of the rabbit. I. Blood counts in normal rabbits. II. Consecutive erythrocyte and hemoglobin observations on groups of normal rabbits. III. Consecutive total white blood cell observations on groups of normal rabbits. *J. Exptl. Med.* 51: 83–97 (Jan.); 52: 23–38, 39–56 (July), 1930.

The results of a statistical analysis of 110 blood counts obtained on 174 normal rabbits with special attention directed to distribution frequencies are reported.

9. BISSONNETTE, T. H. AND WADLUND, A. P. R. Spermatogenesis in *Sturnus vulgaris:* refractory period and acceleration in relation to wave length and rate of increase of light ration. *J. Morphol.* 52: 403–27 (Dec.), 1931.

Birds were exposed to different periods of illumination whereby red, green or white light was used. Testis activity was studied after 5–23 days. Apparatus and mode of light regulation and measurement are described.

10. BAKER, J. R. AND RANSON, R. M. Factors affecting the breeding of the field mouse (*Microtus agrestis*). Part I. Light. *Proc. Royal Soc.* (*London*) *B* 110: 313–22 (Apr.), 1932.

The shortening of the daily period of exposure to light from 15 to 9 hr. almost prevents reproduction in the field mouse, *Microtus agrestis.* The effect is mainly on the females.

11. KUNDE, M. M., GREEN, M. F., CHANGNON, E. AND CLARK, E. Variations in the blood of rabbits from birth to maturity. *Am. J. Physiol.* 99: 463–8 (Jan.), 1932.

The progressive changes in hemoglobin, red blood cells, reticulocytes and hematocrit of the normal rabbit from birth to maturity were determined.

[1] Arrangement is chronological by year of publication. A list of additional references, located in other sections of this bibliography, will be found on page 44.

12. SCARBOROUGH, R. A. The blood picture of normal laboratory animals. (A compilation of published data.) *Yale J. Biol. and Med.* 3: 63–80, 169–79, 267–82, 359–73, 431–40, 547–52, 1930–31; 4: 69–82, 199–206, 323–44, 1931–32.

On the basis of 629 literature references normal blood counts are reported for rabbit, guinea pig, rat, mouse, cat, dog, horse, pig, cattle, monkey, birds. The technique of obtaining blood is described for each animal species. Data are tabulated for erythrocytes, hemoglobin, leukocytes, differential counts, hemolysis, blood volume, coagulation time, specific gravity. Physiological variations as to age, sex, pregnancy, alimentation, anesthetization and breed are also reported.

13. HARTMAN, C. G. AND STRAUS, W. L., JR., ed. *The Anatomy of the Rhesus Monkey* (Macaca mulatta). Baltimore, Williams & Wilkins, 1933, 383 pp.

The book contains chapters on growth and development, skin, skeleton, teeth, muscular, respiratory, digestive, urinary, reproductive and vascular systems, endocrines, nerves, eyes and ears. In an appendix housing and care are described.

14. OGLE, C. AND MILLS, C. A. Animal adaptation to environmental temperature conditions. *Am. J. Physiol.* 103: 606–12 (Mar.), 1933.

Rabbits were subjected for 6 wk. either to a cold room (52°–6°F), or a hot room (88°–92°F) or for 16 hr/day to the hot room and for 8 hr/day to the cold room. Animals adapted to constant heat lost to a considerable degree their ability to produce heat and keep warm under chilling emergencies while those adapted to cooler environment were more able to adapt to chilling conditions but succumbed more readily to excessive heat. A few hours' cooling each day kept the metabolism responsive to chilling.

15. OGLE, C. AND MILLS, C. A. Adaptation of sexual activity to environmental stimulation. *Am. J. Physiol.* 105: 76–7 (July), 1933.

Groups of white mice of a single stock were kept at temperatures of 60°–4°F and 88°–92°F, respectively. In those raised in the cold room the estrous cycle began earlier than in mice in the hot room. Mice seem to adapt poorly to the more severe stimulation of frequent change from hot to cold.

16. OGLE, C. Climatic influence on the growth of the male albino mouse. *Am. J. Physiol.* 107: 635–40 (Mar.), 1934.

Mice adapted to a steady cool environment increased in body weight and body length at practically the same rate as control mice. However, these cold-room mice had tails fully 1 cm shorter than those of the control-room males. Mice subjected to continuous moist heat had exceptionally short slender bodies, the tails of each being 1 cm longer than the body. A changeable environment retarded the growth of male mice, but, at a late age, such animals attained both great body and tail lengths. (Author's summary; exact temperatures were not given.)

17. KELLY, J. W. AND DEARSTYNE, R. S. Hematology of the fowl. *A.* Studies on normal chick and normal adult blood. *B.* Studies on the hematology of chicks suffering from pullorum infection and on adult carriers of pullorum disease. *Agr. Expt. Station, North Carolina State Coll. Agriculture and Engineering, Techn. Bull.* No. 50, Oct. 1935, 69 pp.

In part *A* body temperatures and numerical and differential blood counts of normal chicks, 1–19 days old, are tabulated. In part *B* a technique for inoculating chicks for blood studies is reported. Temperature, weight and blood count charts are given for chicks artificially infected with pullorum disease.

18. REIGHARD, J. AND JENNINGS, H. S. *Anatomy of the Cat.* 3rd ed. New York, Holt, 1935, 486 pp.

Part I of the book on descriptive anatomy of the cat deals with the skeleton, muscles, viscera, circulatory system and sense organs. In part II tabular summaries are given of the skeletal system, skull foramina, muscle innervation, cranial nerve and brachial, lumbar and sacral plexus distribution, arterial and venous systems. In part III directions for dissection and study of the cat are given.

19. BISSONNETTE, T. H. Sexual photoperiodicity. Influence of varying quantities and qualities of light on sexual activity in plants and animals an example of the interaction of genetic and environmental factors in conditioning the expression of characters. *J. Heredity* 27: 171–80 (May), 1936.

Sexual photoperiodism in plants and animals is discussed on the basis of 105 references.

20. BROOK, G. B. *Experimental and Clinical Studies of the Spine of the Dog.* London, Balliere, 1936, 122 pp.

21. KAPPERS, C. U. A., HUBER, G. C. AND CROSBY, E. C. *The Comparative Anatomy of the Nervous System of Vertebrates, Including Man.* New York, Macmillan, 1936, 2 vols., 1845 pp.

The books contain the following chapters: Evolution and morphology of nervous elements; comparative anatomy of the spinal cord; medulla oblongata; lateral line and acoustic systems; effectory system of midbrain and medulla oblongata; coordinating apparatus; cerebellum; mesencephalon and diencephalon; submammalian telencephalon; development of cortex in mammals. Vertebrates discussed are amphioxus, cyclostomes, plagiostomes, ganoids, teleosts, amphibians, reptiles, birds, mammals. An extensive bibliography is included.

22. LENTZ, W. J. General characteristics of the teeth of dogs. *Univ. Penn. Bull.* 36: 3–11 (Jan. 15), 1936.

A treatise on normal teeth and dental diseases.

23. OGLE, C. L. Germinal response (in male mice) to environmental conditons. *Am. J. Physiol.* 117: 285–91 (Oct.), 1936.

The germinating epithelium of male mice kept under conditions of constant humid heat undergoes degeneration, accompanied by giant cell formation. Few actively proliferating tubules are present between the ages of 4 and 12 mo., although the testes reside in deeply pendant scrotal sacs. Mice adapted to an invigorating environment retain their testes intra-abdominally and have active germinal tissue. Submission of such males to humid heat leads to an abrupt degeneration of the testes. Control mice show a similar reaction to humid heat. Microscopic studies of the testes verify the fertility findings previously reported. (From author's summary)

24. WINTROBE, M. M., SHUMACKER, H. B., JR. AND SCHMIDT, W. J. Values for number, size and hemoglobin content of erythrocytes in normal dogs, rabbits and rats. *Am. J. Physiol.* 114: 502–7 (Jan.), 1936.

Data for mean, standard deviation and coefficient of variation of erythrocytes, hemoglobin, packed red cell and mean corpuscular

volume were calculated from 173 blood examinations in 54 dogs, 168 blood examinations in 61 rabbits and 109 determinations in 73 rats. Literature reports relating to these data are summarized. Blood counts of male and female dogs, rabbits and rats are compared.

25. Bruner, H. D. and Wakerlin, G. E. The blood picture of the normal dog. *Proc. Soc. Exptl. Biol. Med.* 36: 667–70 (June), 1937.

The results of 251 determinations of the red blood cell count, hemoglobin, volume of packed red cells, mean corpuscular volume, hemoglobin, and hemoglobin concentration, reticulocyte percentage and leukocyte count of 34 normal dogs are recorded. No significant sex differences for these values were observed. (Author's summary)

26. Cox, W. M., Jr. and Mueller, A. J. The composition of milk from stock rats and an apparatus for milking small laboratory animals. *J. Nutrition* 13: 249–61 (Mar.), 1937.

An automatic milking device is described. The composition of rat milk at various stages of lactation (8th–24th day) was determined; studies on the protein distribution in rat milk are reported and a comparison is given of the composition of rat, cow and human milk.

27. Dukes, H. H. *The Physiology of Domestic Animals.* 4th ed. Ithaca, N. Y., Comstock Pub. Associates, 1937, 695 pp.

The material is distributed into the following chapters: The circulating fluids of the body; circulation of the blood; respiration; digestion and absorption; kidneys and urine, skin; metabolism and heat regulation; endocrine organs; muscle and nerve; central nervous system; special senses; reproduction.

28. Francis, L. D. and Strong, L. C. Hemoglobin studies on the blood of female mice of the CBA strain: effects of age, diet, strain, and reproduction. *Am. J. Physiol.* 124: 511–6 (Nov.), 1938.

Hemoglobin values were determined on the blood of 829 normal inbred mice of the CBA strain at 40-day intervals, from 40–80 days of age in the case of virgins, and from 120–920 days for breeders. Feeding fox chow for several generations gave higher levels of hemoglobin than was found in the same strain of mice maintained similarly on a ration consisting of an oatmeal mixture. Age, diet, and strain should each be taken into account in interpreting data dealing with concentrations of hemoglobin in the blood of mice. (From author's summary)

29. Hagquist, C. W. Cellular changes in the anterior hypophysis during the reproductive cycle in the female guinea pig. *Anat. Record* 72: 211–29 (Oct. 25), 1938.

The hypophyses of 38 adult female guinea pigs were studied at 8 different stages during the reproductive cycle. Twenty of the animals were of known age and all were under continuous, day and night observation from 1 to 15 cycles. The beginning of heat was determined by the copulatory response. At each stage the percentage of cell types, extent of granulation, Golgi apparatus and mitochondria were studied. The hypophyseal picture was also referred to the ovarian conditions.

30. McCrady, E. *The Embryology of the Opossum.* (*Am. Anat. Memoirs* No. 16) Philadelphia, Wistar Institute of Anatomy and Biology, 1938, 233 pp.

31. Schmidt, I. G. and Schmidt, L. H. Variations in the structure of adrenals and thyroids produced by thyroxine and high environmental temperatures. *Endocrinology* 23: 559–65 (Nov.), 1938.

Male and female guinea pigs were exposed to a moderate room temperature (20°C), and to 32°C and a high humidity, for 2–6 weeks. Adrenals and thyroids were studied after ingestion of thyroxine and in untreated animals. Adrenals varied chiefly in the degree of mitotic activity of the cortex and the distribution of the mitoses. (From author's summary)

32. Shukers, C. F., Langston, W. C. and Day, P. L. Normal blood picture of young rhesus monkey. *Folia Haematol.* 60: 416–24, 1938.

The normal blood picture of young rhesus monkey is reported, based upon data obtained in about 150 determinations of total erythrocyte, platelet, reticulocyte, leukocyte and differential counts, hemoglobin, hematocrit, and clotting time determinations upon 19 healthy animals. The middle 68% of data fell into the following ranges: volume of packed cells 36%–44%, hemoglobin 10.9–13.5 gm/100 cc, erythrocytes 4,600,000–5,800,000/cu mm, reticulocytes 0.5%–0.7%, leukocytes 9,700–20,500/cu mm, neutrophils 20%–52%, lymphocytes 44%–74%, platelets 318,000–632,000/cu mm, clotting time 32–124 sec. (From author's summary)

33. Walker, A E. *The Primate Thalamus.* Chicago, Univ. of Chicago Press, 1938, 321 pp.

34. Gregersen, M. I. and Stewart, J. D. Simultaneous determination of the plasma volume with T-1824, and the "available fluid" volume with sodium thiocyanate. *Am. J. Physiol.* 125: 142–52 (Jan.), 1939.

Directions for carrying out simultaneous determinations of plasma volume with the blue dye, T-1824, and of "available fluid" with thiocyanate are briefly outlined. The results of preliminary tests show that these methods may be combined without affecting the accuracy of either the T-1824 or the thiocyanate analysis. By determining the thiocyanate (as ferric thiocyanate) as well as the dye concentration with a spectrophotometer, both analyses may be completed on 0.5 cc of serum. Results of the tests on dogs are tabulated. Large individual differences in both plasma volume and "available fluid" per kg body weight were found. (Condensed from author summary)

35. King, H. D. *Life Processes in Gray Norway Rats During Fourteen Years in Captivity.* Philadelphia, Wistar Institute of Anatomy and Biology, 1939, 77 pp.

Data for life processes in the 11th to 25th generation of wild gray rats (*Rattus norvegicus*) born in captivity at the Wistar Institute are given. Growth and variability in body weight, reproductive period, fertility, sterility, litter size, sex ratio, mortality, behavior, and mutations are discussed.

36. Mills, C. A. and Ogle, C. Ease of body heat loss as a basic developmental and functional factor in warm-blooded animals. *Am. J. Physiol.* 125: 36–40 (Jan.), 1939.

Young white mice were kept in 4 kinds of experimental rooms: *1*) at moist heat: 89°–92°F, 60%–70% humidity and rigid insulated walls; *2*) moist heat-radiant cooling: temperatures and humidity as (*1*) and Al foil insulated walls; *3*) cold air-radiant heating 32°–76°; *4*) air-cooled: 66°–70°. Growth was recorded at 3, 10 and 15 wk. of age, as well as average number/litter. Results show that these basic metabolic factors are dependent

on the ease with which the body can dissipate heat whereby the avenue of heat loss is unimportant.

37. CRILE, G. AND QUIRING, D. P. A record of the body weight and certain organ and gland weights of 3690 animals. *Ohio J. Sci.* 40: 219–59 (Sept.), 1940.

Data are given for invertebrates, amphibia, birds, carnivores, pinnepedia, cetacea, chiroptera (bat), edentates, fish, insectivores, primates, anthropoids, reptiles, rodents, ungulates.

38. OLSON, W. H. Natural isohemagglutination in dogs. *Am. J. Physiol.* 131: 203–9 (Nov.), 1940.

The blood plasma of dogs contains natural isohemagglutinins which are absent in the blood serum. Complete removal of fibrinogen from the plasma removes the property of hemagglutination. Those erythrocytes in the dog that are agglutinable are the most fragile cells. It is believed that dogs may be divided into blood groups. (Author's summary)

39. PYLE, N. J. Use of ferrets in laboratory work and research investigations. *Am. J. Public Health* 30: 787–96 (July), 1940.

The anatomy, physiology, breeding, feeding, housing, and diseases of the ferret, a member of the weasel family, is described. Techniques of inoculation and blood collecting are reported.

40. CRAFTS, R. C. The effects of endocrines on the formed elements of the blood. II. The effect of estrogens in the dog and monkey. *Endocrinology* 29: 606–18 (Oct.), 1941.

The figures for the cellular blood picture of normal female adult dogs, 9–10 kg body wt., are as follows: erythrocyte count 6–7 million cells/cu mm, total white cell count 5–15 thousand cells/cu mm, neutrophils 68.3, eosinophils 4.4, basophils 0.01, lymphocytes 19.1, monocytes 4.8, other types 2.5%. The figures for the cellular blood picture of spayed adult female rhesus monkeys, 4–5 kg body wt., are: erythrocyte count 5–6 million cells/cu mm, total white cell count 10–15 thousand cells/cu mm. Reports in the literature on the total white cell count and the differential count of monkey blood are tabulated. A marked response of the lymphocytes to any excitement of the animal is noted.

41. FISKE, V. M. Effect of light on sexual maturation, estrous cycles, and anterior pituitary of the rat. *Endocrinology* 29: 187–96 (Aug.), 1941.

Immature female rats kept in the light from birth or from the 21st day of life came into sexual maturity 6 days earlier than those kept under normal laboratory conditions and 16 days earlier than females kept in darkness. Weights of reproductive organs of males and females under different conditions of light are given.

42. KROGH, A. *The Comparative Physiology of Respiratory Mechanisms.* Philadelphia, Univ. of Pa. Press, 1941, 172 pp.

The book contains chapters on the call for and the acess to oxygen, forces acting in the transport of O_2 and CO_2 through living tissues, respiration in water, emergency respiration, respiration in air, respiratory functions of blood, tracheal respiration.

43. RUCH, T. C. *Bibliographia Primatologica.* New Haven, Yale Medical Library, 1941, 241 pp.

A classified bibliography on primates is presented, including anatomy, embryology, quantitative morphology, physiology, pharmacology, psychobiology, primate phylogeny and miscellanea. (4,630 references)

44. SNELL, G. D., ed. *Biology of the Laboratory Mouse.* Philadelphia, Blakiston, 1941, 497 pp.

The book contains the following chapters: Early embryology of the mouse; reproduction; histology; spontaneous neoplasms in mice; gene and chromosome mutations; genetics of spontaneous tumor formation; genetics of tumor transplantation; endocrine secretion and tumor formation; milk influence in tumor formation; inbred and hybrid animals and their value in research; parasites; infectious diseases of mice; care and recording.

45. GRIFFITH, J. Q., JR. AND FARRIS, E. J., ed. *The Rat in Laboratory Investigation.* Philadelphia, Lippincott, 1942, 488 pp.

The book contains chapters on breeding, anatomy, physiology, dietary requirements, metabolism, hematology, x-ray and histologic techniques, handling, exposure techniques, anesthesia, and diseases.

46. HORSBURGH, D. B. AND HEATH, J. P. *Atlas of Cat Anatomy.* 3rd ed. Stanford, Calif., Stanford Univ. Press, 1942, 40 pp.

Skeletal system; muscular system; nervous system; vascular system; digestive system; urogenital system.

47. MILLS, C. A. AND SCHMIDT, L. H. Environmental temperatures and resistance to infection. *Am. J. Trop. Med.* 22: 655–60 (Nov.), 1942.

White mice maintained at environmental temperatures of 66°–8°F and 90°–1°F, respectively, after 3 wk. showed rectal temperatures of 99.26° ± 0.08° and 99.91° ± 0.06°F, respectively. This difference of 0.06° is considered statistically significant. When mice unadapted to heat were subjected to 96°F for 2 days, their rectal temperature increased to 104.4°F. After Type I pneumococcus inoculation mice kept at 65°F had a mean survival time of 44.9 hr., those at 75°F survived 36.3 hr. and those at 90°F only 27.5 hr.

48. CHAMBERLAIN, F. W. *Atlas of Avian Anatomy. Osteology, Arthrology, Myology.* East Lansing, Mich., Michigan State College, Agricultural Experiment Station, 1943, 213 pp.

49. COURTICE, F. C. The blood volume of normal animals. *J. Physiol.* (*London*) 102: 290–305 (Dec.), 1943.

The blood volume of a series of normal, healthy, unanesthetized rabbits, dogs, goats and horses has been estimated with the blue dye T-1824. The mean values for 60 rabbits, 29 dogs, 30 goats and 2 horses are respectively: plasma volume 50, 54, 53 and 51 cc/kg body weight, and blood volume 70, 79, 70 and 72 cc/kg. The blood volume of 4 highly trained greyhounds was much higher due to a higher cell volume. (Condensed from author's summary)

50. DAVIS, J. E. Erythrocyte longevity in dogs and rabbits. *J. Lab. Clin. Med.* 28: 848–50 (Apr.), 1943.

The minimal average life duration of erythrocytes in dogs and rabbits has been calculated on the basis of data on the rate of depression of experimental erythropoiesis in polycythemic animals by liver or vasodilator drugs. The life spans thus obtained were 20 days in the dog and 22.4 days in the rabbit.

51. VAN LOON, E. J. AND CLARK, B. B. Hematology of the peripheral blood and bone marrow of the dog. *J. Lab. Clin. Med.* 28: 1575–9 (Oct.), 1943.

A summary and statistical analysis of the data on the peripheral blood hematology of 81 dogs are presented. Differential cell counts of rib and femur marrow preparations from 8 dogs are included. (Author's summary)

52. Baker, G. A. and Kleiber, M. Characteristics of the daily weights of sexually mature rats on a constant diet. *Growth* 8: 159–67 (June), 1944.

The daily weights of female rats, 89–105 days old, fed on a constant normal ration under standard laboratory management, can be expressed as a trend that can be represented by a polynomial, plus a periodic component that can be represented by 1 sine curve or by the combination of 2 sine curves, plus a part that is nearly but not quite random. (Condensed from author's summary)

53. Metcoff, J. and Favour, C. B. Total circulating protein and hemoglobin in the growing rat. *Am. J. Physiol.* 142: 94–103 (Aug.), 1944.

The concentration of hemoglobin, erythrocytes and plasma proteins was determined in young pubescent and mature Sherman strain rats. Blood volume partition studies, using the dye T-1824, were done concurrently. Based on these studies the total circulating plasma protein and hemoglobin was calculated. The values so obtained are possibly more relative than absolute but afford some insight into the dynamic adjustments occurring with growth in the rat.

54. Bloom, F. Bone marrow biopsies in normal and diseased dogs—differential cell counts. *J. Am. Vet. Med. Assoc.* 57: 220–5 (Oct.), 1945.

Two principal methods of obtaining bone marrow from living dogs are described, the trephine method and the method of aspirating marrow from the crest of the ilium. Average blood and marrow findings are reported for normal dogs and dogs with diseases such as pyometra, streptotrichosis, subacute suppurative peritonitis, fibrosis of the pancreas, nervous distemper, advanced filariasis, regenerative anemia and malignant lymphoma. The blood count included erythrocytes, hemoglobin, differential white cell count.

55. Endicott, K. M. and Ott, M. The normal myelogram in albino rats. *Anat. Record* 92: 61–9 (May), 1945.

The hemogram and myelogram of albino rats of 2 age groups (> 60 days old, < 60 days old) are presented. Values are tabulated for hematocrit, total leukocytes, neutrophils, eosinophils, lymphocytes and nuclear red cells in the peripheral blood and bone marrow smears. In rats below 1 mo. of age the marrow was found to be predominantly erythropoietic, while in those over 2 mo. of age the marrow was predominantly granulocytopoietic. A modification of Kindred's method of estimating the relative volume of active marrow and a simple apparatus for sketching from projected microscopic slides are described.

56. Graves, A. P. Development of the golden hamster, *Cricetus auratus Waterhouse*, during the first nine days. *Am. J. Anat.* 77: 219–51 (Sept.), 1945.

The early developmental stages of the golden hamster (*Cricetus auratus*) are described on the basis of the study of 178 embryos, which were preserved at close intervals up to the middle of the 9th day. The hamster is remarkable for precocity of reproduction in the female sex. The eggs are relatively large and contain considerable amounts of formed yolk. The hamster is the fastest developing mammal so far known. A comparison is made of the general course of development of the hamster with that of the opossum and of the rat. Many features of its development characterize the hamster as a primitive member of the murid family, and as comparatively closely related to geomyid rodents. (Author's summary)

57. Hale, C. W. Colour and growth of hair in rabbits. *Nature* 155: 670–1 (June 2), 1945.

Observations of hair growth in rabbits with colored hair and in albino rabbits seem to indicate that both rapid growth and natural pigmentation of the hair shaft are correlated with local increased blood supply to the hair follicles.

58. Medoff, H. S. and Bongiovanni, A. M. Age, sex and species variations on blood pressure in normal rats. *Am. J. Physiol.* 143: 297–9 (Jan.), 1945.

Blood pressures were determined in 130 Wistar albino rats and 33 Wistar gray Norway rats. The animals were maintained under a fixed and standard depth of ether anesthesia. The albino rats showed a definite tendency toward higher blood pressures with increasing age. While at 110–140 days of age 80% had blood pressure levels of less than 139 mm Hg, this percentage dropped to 11.1 at age 825–910 days. No sex differences were noted.

59. Mills, C. A. Influence of environmental temperatures on warm-blooded animals. *Ann. N. Y. Acad. Sci.* 46: 97–105 (June 15), 1945.

The effect of temperature on metabolic rate, growth, development, onset of sexual functions and fertility, carbohydrate metabolism, mental functions, resistance to infection, longevity, drug toxicity and neoplastic tendencies is reviewed.

60. Mulligan, R. M. Quantitative studies on the blood and bone marrow of newborn mongrel puppies. *Anat. Record* 91: 161–7 (Feb.), 1945.

The blood and bone marrow of 21 newborn mongrel puppies, ½ to 2½ days old, were quantitatively studied. The most important finding was a preponderance of erythrocytopoiesis over granulocytopoiesis in the marrow of the puppies. (Condensed from author's summary)

61. Asdell, S. A. *Patterns of Mammalian Reproduction.* Ithaca, N. Y., Comstock Pub. Associates, 1946, 437 pp.

62. Crabb, E. D. *Principles of Functional Anatomy of the Rabbit.* St. Louis, J. S. Swift, 1946, 100 pp.

The book contains chapters on elementary tissues, skeleton, muscules, vascular system, digestive system, nervous system. An extensive bibliography is given.

63. Dietz, A. A. Composition of normal bone marrow in rabbits. *J. Biol. Chem.* 165: 505–11 (Oct.), 1946.

A method for the analysis of bone marrow is described and its composition is given.

64. Fuhrman, G. J., McLin, E. D. and Turner, M. L. The effect of time of day on the metabolic rate of albino mice; a manometric method. *Am. J. Physiol.* 147: 284–8 (Oct.), 1946.

A manometric apparatus for the measurement of individual metabolic rates of small animals is described. Rates of oxygen consumption (Q_{O_2}) of albino mice were determined during the morning and afternoon and the activity of the animals recorded. (Condensed from author's summary)

65. LEWIS, L. A. Changes that occur in plasma proteins during growth of the dog. *J. Biol. Chem.* 162: 473–6 (Mar.), 1946.

The total protein and Tiselius electrophoretic fractions were determined on the plasma of 4 dogs from the time the animals were weaned until they were fully grown. (Condensed from author's summary)

66. MORRISON, P. R. AND PEARSON, O. P. The metabolism of a very small mammal. *Science* 104: 287–9 (Sept. 27), 1946.

Values are given for the minimum, average and maximum rates of O consumption of the shrew, *Sorex cinereus cinereus* Kerr. The basal metabolism of the shrews *Sorex* and *Blarina* is compared with that of other mammals, such as guinea pig and mouse.

67. ROSE, C. L., HANNAH, J. R. AND CHEM, K. K. Cellular constituents and chemistry of the hamster's blood. *Proc. Indiana Acad. Sci.* 55: 190–5, 1946.

A technique of drawing blood from the hamster is described. In order to establish a firm basis for pharmacological experimentation of the Syrian hamster (*Cricetus auratus*) blood cell counts (hemoglobin, erythrocytes, leukocytes, neutrophils, lymphocytes, monocytes and eosinophils) and blood chemical analyses (Ca, P, prothrombin time) were carried out.

68. WILLIAMS, E. M. V. Urea excretion by rabbits. *J. Physiol. (London)* 105: 223–30 (Dec.), 1946.

A method for the collection of urine and its analysis is described and the concentration of urea in urine and blood is given.

69. ZUCKER, T. F. AND ZUCKER, L. M. Bone growth in the rat as related to age and body weight. *Am. J. Physiol.* 146: 585–92 (July), 1946.

Data are presented on the growth of the femur ash and matrix in relation to age and body weight in over 1000 male and female rats from 2 to 750 days of age. Either bone constituent can be estimated from live weight with twice the precision or half the error that would result in an estimate from age. (Author's summary)

70. FRIEDMAN, S. M. AND MARTIN, W. S. The determination of the heart rate in the rat. *J. Lab. Clin. Med.* 32: 1284–7 (Oct.), 1947.

An electric apparatus for the determination of the heart rate in the rat is described. The device also permits the study of heart sounds. Steady and reproducible results were obtained by placing the rats in holders for ½ hr/day and determining the rate on the 3rd day. The normal heart rate in the unanesthetized rat averaged 300/min.

71. GARDNER, M. V. The blood picture of normal laboratory animals. A review of the literature, 1936–46. *J. Franklin Inst.* 243: 77–86 (Jan.), 172–6 (Feb.), 251–8 (Mar.), 434–6 (May), 498–502 (June); 244: 155–61 (Aug.), continuation 48 pp., 1947.

A review of the literature from 1936–1946 on blood studies of the following animals is presented: rat, rabbit, mouse, hamster, guinea pig, monkey, dog, cat, cattle, horse, sheep, swine, fish, birds (chicken, turkey, duck, pigeon, canary). The method of obtaining blood is described for each animal. Blood data included in the review are: reticulocytes, erythrocytes, hemoglobin, leukocytes and differential count, hematocrit, blood volume, sedimentation rate, coagulation time, specific gravity.

72. GUYTON, A. C. Measurement of the respiratory volumes of laboratory animals. *Am. J. Physiol.* 150: 70–7 (July), 1947.

The valve methods and oscilloscopic respirograph method for determining respiratory volume were described. Data on quiet respiration in the following species are presented: mouse, cotton rat, hamster, white rat, guinea pig, rabbit, monkey. Respiratory volume did not vary directly with body weight on body surface, but it varied approximately with the ¾ power of the weight.

73. NICHOLAS, J. S. Experimental approaches to problems of early development in the rat. *Quart. Rev. Biol.* 22: 179–95 (Sept.), 1947.

A review with numerous references.

74. SAWITSKY, A. AND MEYER, L. M. The bone marrow of normal cats. *J. Lab. Clin. Med.* 32: 70–5 (Jan.), 1947.

A method is presented describing the technique for obtaining bone marrow from the iliac crest of the cat by aspiration. Data are given showing the cellular constituents in the peripheral blood and bone marrow of normal cats. A comparison of the bone marrow findings in cats with those of dogs and man is made, utilizing the method of aspiration in all 3 groups. (Author's summary)

75. VOGEL, M. The femoral bone marrow cells of the albino rat. *Am. J. Med. Sci.* 213: 456–62 (Apr.), 1947.

A new technique for obtaining smears of femoral bone marrow of the rat is detailed. The types of cells observed in the femoral bone marrow are described and their interrelationships discussed. On the basis of morphologic studies of the femoral bone marrow in 12 adult albino rats tables have been constructed to show the distribution by percentage of the various cellular elements; the range and modal values for each have been determine. (Author's summary)

76. WEBSTER, S. H., LILJEGREN, E. J. AND ZIMMER, D. J. Organ:body weight ratios for liver, kidneys and spleen of laboratory animals. I. Albino rat. *Am. J. Anat.* 81: 477–513 (Nov.), 1947.

The normal variation in the post-mortem relative weights of the liver, kidneys and spleen of male and female albino rats of 12 weight groups was determined on 461 animals of the Sprague-Dawley and Wistar strains. (Condensed from author's summary)

77. EL HINDAWY, M. R. The blood cells of normal dogs. *Vet. J.* 104: 194–8 (Feb.), 1948.

Blood counts (erythrocytes, leukocytes, hemoglobin) are reported for normal young, adolescent and adult dogs of both sexes. (Condensed abstr. *J. Am. Vet. Med. Assoc.* 113:59 (July), 1948)

78. NICHOLS, J. AND MILLER, A. T., JR. A comparison of the total leukocyte count in the heart blood and peripheral blood of the rat. *Science* 108: 378–9 (Oct. 8), 1948.

Total leukocyte counts were made on Wistar male albino and on mongrel rats, using standard methods and Bureau of Standards certified equipment. No statistically significant difference was found between counts of the heart blood and tail blood.

79. QUIMBY, F. H., SAXON, P. A. AND GOFF, L. G. Total white cell counts of peripheral and heart blood of the rat. *Science* 107: 447 (Apr. 30), 1948.

Total white cell counts of heart and tail blood were performed on male albino rats. While the red cell numbers and density of

the blood taken from the 2 sources showed the same values, the white cell count was considerably smaller in heart blood. This difference might probably be concerned with the immunity functions of the leukocytes.

80. ADOLPH, E. F. Quantitative relations in the physiological constitutions of mammals. *Science* 109: 579–85 (June 10), 1949.

Interrelations are derived from specific data representing the rates of particular physiological processes. These interrelations apply also to sizes of organs, numbers of reduplicated structures and biochemical compositions. Some 34 correlatives in mammals are presented nomographically so that from a measurement of any one property the 33 others can be read.

81. BENSLEY, B. A. *Practical Anatomy of the Rabbit. An Elementary Laboratory Text-Book in Mammalian Anatomy.* 8th ed., revised and edited by CRAIGIE, E. H. Philadelphia, Blakiston, 1949, 391 pp.

Structure, osteology and dissection of the rabbit are covered.

82. EDERSTROM, H. E. Comparison of RBC counts in central and peripheral blood in various laboratory animals. *Proc. Soc. Exptl. Biol. Med.* 70: 172–3 (Feb.), 1949.

Red cell counts of blood secured from peripheral vessels were compared to counts from the heart or large vessels in the rat, mouse, hamster, rabbit, guinea pig, and dog. In none of these was a statistically significant difference found. (Author's summary)

83. FARRIS, E. J. *Anatomy and Physiology Laboratory Guide.* 5th ed. Philadelphia, Lippincott, 1949, 146 pp.

The guide refers to the anatomy and physiology of man. In the appendix a list of films is given including several on laboratory animals such as: Tumor cells and macrophages in tissue cultures; rat sarcomas and carcinomas; development of the opossum; of a salamander; early development of rabbit egg; ovulation in the frog, *Rana pipiens*; parturition in the rhesus monkey; reproduction among mammals; where chick life begins.

84. WEBSTER, S. H. AND LILJEGREN, E. J. Organ:body weight ratios for certain organs of laboratory animals. II. Guinea pig. *Am. J. Anat.* 85: 199–230 (Sept.), 1949.

The normal variation in the post-mortem relative weights of the liver, kidneys and spleen of male and female guinea pigs of 7 weight groups was determined on 235 animals of a mongrel inbred strain ranging in body weight from 61 to 1,279 gm. The weights of heart and lungs were also determined on 106 of these animals. (Condensed from author's summary)

85. HEDIGER, H. *Wild Animals in Captivity.* London, Butterworth & Co., 1950, 207 pp.

Contents cover: Territorial requirements in the wild state; sociological factors in the wild state; from freedom to captivity; range in the wild state; the problem of confined space; escapes; quality of the environment; exogenous factors: biological environment; the problem of food; the animal's relationship with man.

86. LATIMER, H. B. The weights of the brain and of its parts and the weight and length of the spinal cord in the adult male guinea pig. *J. Comp. Neurol.* 93: 37–51 (Aug.), 1950.

The usual statistical constants were found for the body weight, body length, weight of the brain and for its 4 major divisions, and the weight and length of the spinal cord in 100 guinea pigs. Empirical formulas are given whereby the above dimensions may be found from either body weight or body length. The variations and correlations of the divisions are presented.

87. MUNN, N. L. *Handbook of Psychological Research on the Rat. An Introduction to Animal Psychology.* Boston, Houghton, 1950, 598 pp.

Some 2,000 papers devoted to studies of the psychology of the laboratory rat are reviewed. The material is arranged according to the following aspects: unlearned behavior, general activity, motives, emotions and hoarding, sensory processes and their role in maze behavior, learning process and its aspects and conditions, systematic psychology, abnormal and social behavior. The use of rats as laboratory animals, purchasing, housing, feeding, breeding, handling, marking and procedures such as split-litter technique, size of groups, etc. are discussed in the introduction.

88. RAVEN, H. C. *The Anatomy of the Gorilla.* New York, Columbia Univ. Press, 1950, 259 pp.

89. SPRAY, C. M. AND WIDDOWSON, E. M. The effect of growth and development on the composition of mammals. *Brit. J. Nutrition* 4 (*No. 4*): 332–53, 1950.

The concentrations of protein, water, fat, Na, K, Ca, Mg, P, Cu and Zn were determined in the bodies, livers and spleens of rats, rabbits, cats, pigs, mice and guinea pigs from birth to maturity, and variations with age and sex were noted.

90. STEVENS, C. D., MEINKEN, M. A., QUINLIN, P. M. AND STEWART, P. H. The distribution of radioactive iodine in mice with and without tumor 15091a after injection of radioactive sodium iodide. *Cancer Research* 10: 155–61 (Mar.), 1950.

The distribution of I^{131} in the tissues of normal mice and mice with implants of tumor 15091a was studied. A table is included showing the weights of organs (blood, spleen, liver, kidneys, lungs, heart, leg muscle, stomach, testes, tumor, thyroid) of control and tumor mice.

91. TREON, J. F. AND RYDER, H. W. Numbers of erythrocytes, leukocytes and types of leucocytes, and content of hemoglobin in peripheral blood of female rabbits. *Am. J. Physiol.* 162: 709–13 (Sept.), 1950.

Values of the elements of the peripheral blood of normal white rabbits are tabulated. A method of analysis is described that may be used to compare this group with any other. (Author's summary)

92. WEST, C. D. AND RAPOPORT, S. Urine flow and solute excretion of hydropenic dog under 'resting' conditions and during osmotic diuresis. *Am. J. Physiol.* 163: 159–74 (Oct.), 1950.

The relation between urine flow and solute concentrations (urea, Na, K, Cl, SO_4, PO_4) in urine and plasma of the dog was studied under resting hydropenic conditions and during osmotic diuresis. The results are tabulated.

93. BÜSING, K.-H. AND GRUCHMANN, W. Untersuchungen über das Blut der Ratte. (The blood of the rat.) *Naunyn-Schmiedbergs Arch. exptl. Pathol. u. Pharmakol.* 212: 251–4, 1951.

The following blood values of black rats were determined: hemoglobin, leukocytes, reticulocytes, differential blood picture of

leukocytes, total protein, albumin, globulin and residual N of blood serum. Rat serum was also tested for normal antibodies against sheep erythrocytes.

94. CRAIGIE, E. H. *A Laboratory Guide to the Anatomy of the Rabbit.* New York, Blakiston, 1951, 113 pp.

The book contains the following chapters: Microscopic anatomy (epithelial, connective, muscular, nervous tissue, blood and lymph); skeleton (general, axial and appendicular subdivision); external features; muscles of the limbs; joints of hip and knee; abdominal wall; digestive and urogenital system; walls of thorax and mechanism of breathing; heart and principal blood vessels; peripheral nerves in the trunk; respiratory organs; muscles of mastication; oral cavity, pharynx and larynx; contents of orbit; spinal cord and spinal nerves; brain. Brief chapters on anatomical terminology and the zoological position of the rabbit are included.

95. EGGLETON, M. G. The state of body water in the cat. *J. Physiol. (London)* 115: 482–7 (Dec.), 1951.

The volume of body water in cats was calculated either from the increase in chloride concentration in the plasma water after injection of hypertonic NaCl solution or by determining the volume of water into which urea was diffused. A value of body water of 63±1.6% body weight was found by the urea method and a value of 49.5±1.08% body weight by the hypertonic NaCl method. The origin of the difference between the 2 values is discussed.

96. FULLER, J. L. Genetic variability in some physiological constants of dogs. *Am. J. Physiol.* 166: 20–4 (July), 1951.

The systolic blood pressure, heart period, cardiac arrhythmia, pupil diameter, maximum pupil contraction and rectal temperature were studied in 133 purebred dogs at 34–39 wk. of age. The breeds represented were basenjis, beagles, cocker spaniels, wirehaired fox terriers and Shetland sheep dogs. The techniques used are briefly summarized. All variables showed a significant difference between breeds.

97. GATZ, A. J. AND HOUCHIN, O. B. Studies on the heart of vitamin E-deficient rabbits. *Anat. Record* 110: 249–66 (June), 1951.

EKG's were taken of normal New Zealand giant rabbits and their littermates on a vitamin E-deficient diet. The findings are discussed.

98. GILLMAN, T. AND PIENAAR, U. DE V. The cytology of the leukocytes in the blood of albino rats and comparisons with leukocytes in the blood of trypan blue-treated rats. *S. African J. Med. Sci.* 16: 61–78 (Nov.), 1951.

The study records findings on the cytology of the lymphocytes, monocytes, and intermediate mononuclear cells, as well as on the neutrophil granulocytes in the blood of control rats studied supravitally with bright field and phase contrast microscopy, and in blood films stained with Romanowsky dyes and treated to demonstrate intracellular peroxidase positive material. Some comparisons were made between the leukocytes found in the blood of control albino rats and some of the white blood cells encountered in the blood of the same strain of rats after prolonged treatment with trypan blue.

99. HAMILTON, J. B., ed. The growth, replacement, and types of hair. *Ann. N. Y. Acad. Sci.* 53: 461–752 (Mar.), 1951.

This series of papers is the result of a conference on Growth, Replacement and Types of Hair, held by the Section of Biology of The New York Academy of Sciences on Feb. 10–11, 1950. The articles contain, among other information, information on hair of mammals other than man, including rats and mice, guinea pigs, rabbits, goats, swine, sheep and cattle.

100. HORT, W. Morphologische und physiologische Untersuchungen an Ratten während eines Lauftrainings und nach dem Training. (Morphological and physiological studies in rats during and after exercise.) *Arch. pathol. Anat. u. Physiol. Virchow's* 320: 197–237 (June 28), 1951.

Young adult white rats were subjected to severe running exercise for 50 days. A bradycardia developed by the 40th day of exercise and disappeared within 40 days after the end of training. During training the weight of the hearts increased by 30%; the weight returned to normal within 4–5 wk. after the end of the training. A method is described for counting the fibers in a given section of the heart.

101. KOLMER, J. S., SPAULDING, E. H. AND ROBINSON, H. W. *Approved Laboratory Technic.* 5th ed. New York, Appleton, 1951, pp. 13–34.

Chapter 2 (Diseases of animals, and methods for the care, inoculation and bleeding of animals) deals with housing, identification, feeding of animals; diseases in guinea pigs, rabbits, mice, rats; inoculation of animals by various routes; technique of postmortem examinations. Normal temperature, pulse and respiration of guinea pig, rabbit, rat and mouse as well as normal blood values and ranges (number and volume of erythrocytes, hemoglobin, platelets, leukocytes, neutrophils, eosinophils, basophils, lymphocytes and monocytes) of domestic and some laboratory animals are tabulated.

102. LATIMER, H. B. Weights, percentage weight and correlations of the endocrine glands of the adult male guinea pig. *Anat. Record* 111: 299–315 (Nov.), 1951.

The weights, percentage weights and the coefficients of variation and/or correlations with body weight and length, and parts of central nervous system are given for the hypophysis, thyroid, suprarenals and testes, taken from 100 young adult male guinea pigs.

103. PETERSEN, E. S., RICKETTS, H. T., BREWER, N. R., LINTS, H. A., TEST, C. E. AND TUPIKOVA, N. A. Electrocardiogram of the beagle dog. *Proc. Soc. Exptl. Biol. Med.* 77: 330–2 (June), 1951.

Unanesthetized and untrained dogs, in a supine position, were tied to the operating table and plate electrodes with ample jelly were applied without shaving. The electrocardiographic patterns observed in 50 tracings taken on 32 normal beagles, 5–28.5 mo. old, 6.0–12.5 kg weight, are described.

104. RUSSELL, E. S., NEUFELD, E. F. AND HIGGINS, C. T. Comparison of normal blood picture of young adults from 18 inbred strains of mice. *Proc. Soc. Exptl. Biol. Med.* 78: 761–5 (Oct.–Dec.), 1951.

Erythrocyte count, hematocrit determination, hemoglobin content, reticulocyte percentage, total leukocyte count, and proportion of granulocytes were determined in the blood of 2–3-mo.-old virgin males and females of 18 different inbred strains. The means and standard errors for each determination are given for each strain. Although there was considerable overlap among the strains, it was possible by analysis of variance to show that there were significant genetic differences among the strains in factors affecting erythrocyte number (as shown both in count and hemato-

crit), and mean erythrocyte volume (one case only), total leukocyte count, and proportion of granulocytes. Mean total leukocyte count for a strain was negatively correlated with proportion of granulocytes. (From author's summary)

105. ALGERIA. Inspection générale de l'agriculture. 1952. Réflexe optohypophysaire. (General inspection of agriculture. 1952. Optohypophysial reflex.) *Rapp. Cons. Exp. Rech. agron. Insp. gén. Agric.* (*Algeria*) 1951–52: 179–80.

The milk secretion of female rats, as measured by the 3-wk.-old live weight of their young, was greater in animals kept in a red light than in those in a green light or in daylight. (*Animal Breeding Abstr.* 23: 278 (March), 1955; the number of experimental animals involved is not given.)

106. BURSTEIN, S. The guinea pig as a laboratory animal for corticoid excretion studies: modification of the formaldehydogenic method. *Endocrinology* 50: 412–8 (Apr.), 1952.

Use of the guinea pig for the study of urinary corticoids and adrenocortical activity is demonstrated. Urinary corticoid in male guinea pigs averaged 140 μg for a 17-hr. urine sample by the phosphomolybdic acid method and 45 μg by the formaldehydogenic method. Compared with the human adult on the basis of body weight, the guinea pig excretes about 10 times the quantity of corticoids.

107. CALHOUN, J. B. The social aspects of population dynamics. *J. Mammalogy* 33: 139–59 (May), 1952.

A variety of phenomena relating to the interrelationship between sociality and population dynamics are discussed. Reference is made to, among other animals, the rat, mouse, dog, rabbit, monkey and opossum.

108. EVERETT, N. B. Early postnatal changes in pulmonary blood volume of the guinea pig. *Am. J. Physiol.* 169: 34–9 (Apr.), 1952.

The changes in pulmonary blood-volume/unit-weight of lung have been determined in guinea pigs at intervals ranging from 5 min. to 7 hr. after birth. The blood of fetuses was labeled with radioiron and the radioactivity of lung tissue between breathing and nonbreathing littermates was compared. (Condensed from author's summary)

109. FERRINI, O. AND GAMBARO, C. G. Studi sull'equilibrio idrosalino plasmatico e tissurale. Distribuzione dell'acqua e dei sali nel plasma e nel muscolo di coniglio, cavia e ratto normali, studiata con il metodo della spettrofotometria a fiamma. (Water-salt equilibrium in plasma and tissues. Distribution of water and salts in normal rabbit, guinea pig, and rat plasma and muscle as determined by flame spectrophotometry. *Arch. "E. Maragliano" patol. e clin.* 7: 1085–1110 (Nov.–Dec.), 1952.

The contents of K, Na, Cl, and H_2O in the plasma and skeletal muscle of the rabbit, guinea pig and rat were determined.

110. GRÜNEBERG, H. *The Genetics of the Mouse.* 2nd ed. The Hague, Nijhoff, 1952, 650 pp.

The following chapters are included: Taxonomy; reproduction and growth; the integument: the inheritance of coat color, spotting, skin and hair structure; endocrine organs; central nervous system; the eye; blood and blood-forming organs; the skeleton; alimentary tract and respiratory organs; urogenital system, mammary glands; quantitative differences; the resistance to infectious diseases; the genetics of cancer; chromosomal inheritance; induced genetic changes; gene action in the mouse. A bibliography with 1,751 references, arranged according to subjects, is included.

1111. HARTMAN, C. G. *Possums.* Austin, Univ. of Tex. Press, 1952, 174 pp.

The life history of the opossum from a nontechnical view is presented. Included are chapters on embryology and reproduction.

112. LEACH, W. J. *Functional Anatomy of the Mammal. A Guide to the Dissection of the Cat and an Introduction to the Structural and Functional Relationship Between the Cat and Man.* 2nd ed. New York, McGraw, 1952, 276 pp.

The book contains chapters on the skeletal system, voluntary muscles, internal anatomy, alimentary, respiratory, vascular, urogenital and nervous systems, special sensory apparatus, endocrine organs. In the appendix, laboratory preparation and preservation of materials are discussed.

113. MILLER, M. E. *Guide to the Dissection of the Dog.* 3rd ed. Edwards, Ann Arbor, Mich., 1952, 369 pp.

The book contains chapters on the skeletal and muscular system; thorax, neck and pectoral limb; abdomen, pelvis and pelvic limb; head; central nervous system and articulations.

114. NATIONAL RESEARCH COUNCIL, COMMITTEE ON THE HANDBOOK OF BIOLOGICAL DATA. *Standard Values in Blood*, edited by E. C. ALBRITTON. Philadelphia, Saunders, 1952, 199 pp.

Tables are presented on the following subjects: Physical properties; coagulation phenomena; blood groups; erythrocytes and hemoglobin; leukocytes; blood and bone marrow cells; water, carbohydrate, lipid, protein; amino acids, nonprotein nitrogen; phosphorus, sulfur; vitamins, hormones, enzymes; electrolytes, minerals, gases, acid-base; effects of radiation, storage; therapeutic agents. Data are given for man and farm and laboratory animals. An extensive bibliography is included.

115. PROSSER, L. ed. *Comparative Animal Physiology.* Philadelphia, Saunders, 1952, 888 pp.

The book contains the following chapters: Water; inorganic ions; protein specificity; nutrition; feeding and digestion; nitrogen excretion; respiration and metabolism; respiratory functions of body fluids; temperature: metabolic aspects and perception; photoreception; chemoreception; phonoreception; mechano-and equilibrium-reception; circulation of body fluids; muscle and electric organs; amoeboid movement; cilia; trichocysts and nematocysts; bioluminescence; chromatophores and color change; endocrine mechanisms; nervous systems.

116. SOLIMAN, F. A. AND REINEKE, E. P. Influence of variations in environmental temperature and thyroid status on sexual function in young female mice. *Am. J. Physiol.* 168: 400–5 (Feb.), 1952.

The average body weights (gm) and the weights of ovary and uterus (mg/100 gm body weight) of mice, produced from Rockland Farms, after being kept for 4 wk. at different temperatures were given as follows: (24°C) 20.65±0.92, 37.49±3.36, 103.72±12.10; (30°C) 21.83±0.59, 32.91±4.73, 87.34±4.36; (35°C) 21.39±0.93, 40.16±3.56, 135.81±24.03, respectively. The corresponding data for another shipment of mice, maintained for

4 wk. at 24°C, were 23.43±1.00, 20.00±1.83 and 202.82±15.18, respectively.

117. Ambrus, J. L., Ambrus, C. M. and Harrisson, J. W. E. Gastric acid secretion and gastric ulcer formation of rats and guinea pigs. *Am. J. Physiol.* 173: 95–9 (Apr.), 1953.

The procedure of testing gastric secretion in rats and guinea pigs and of analyzing the gastric juice is described. Data for interdigestive gastric secretion in normal rats and guinea pigs, respectively, are given as follows: gastric juice volume, ml: 1.2, 0.75; acidity, ml equiv. N/10 HCl/100 ml, total, 77, 29; free, 40, 0.

118. Anghi, C. Kísérlet az alkati szilárdság meghatározására házinyúlnál. (Constitutional strength of domestic rabbits.) *Allattenyésztés* 4: 366–73, 1953.

Constitutional strength measured by resistance to thirst was greatest in Chinchillas, least in Vienna Blues and intermediate Angoras. It is suggested that this method of measuring constitutional strength should be applied to other species of livestock. (*Animal Breeding Abstr.* 23: Abstr. No. 275 (Mar.), 1955)

119. Bartlett, R. G., Jr., Helmendach, R. H. and Bohr, V. C. Effect of emotional stress, anesthesia, and death on body temperature of mice exposed to cold. *Proc. Soc. Exptl. Biol. Med.* 83: 4–5 (May), 1953.

When adult Swiss albino mice, both restrained and unrestrained, were exposed to cold, the unrestrained animals experienced a small drop in body temperature while in the restrained ones body temperature dropped to the death point. Anesthetized unrestrained mice exposed to cold demonstrated still greater temperature drops than conscious restrained mice. Conditioning by maintaining the mice in restraining cages 1 hr/day, resulted in a lesser drop of body temperature and decreased mortality. It was concluded that emotional hypothermia can be produced in mice by the stress of confinement.

120. Bartlett, R. G. and Register, U. D. Effect of cold and restraint on blood and liver non-protein sulfhydryl compounds. *Proc. Soc. Exptl. Biol. Med.* 83: 708–9 (Aug.–Sept.), 1953.

Liver and blood ergothioneine, glutathione and total non-protein sulfhydryl concentrations were determined in normal mice at 22°C and in restricted and unrestricted ones at 0°C.

121. Becks, H. and Evans, H. M. *Atlas of the Skeletal Development of the Rat.* Berkeley, Calif., American Institute of Dental Medicine, 1953, 145 pp.

The work establishes precise standards for the growth of the skeleton of rats. The standards are for the Long-Evans strain, developed on the Berkeley campus and widely used in this country for experiments in growth. The atlas consists of 145 pages of photographs and x-ray pictures showing in microscopic detail the changes that occur in bone tissue at different stages of development, from 1 to 1,316 days of age, of both normal rats and those which have had their pituitary glands removed. (From a review in *Science* 119: 346 (Mar. 12), 1954)

122. Brace, K. C. Life span of the marmot erythrocyte. *Blood* 8: 648–50 (July), 1953.

A simplified technique using C^{14}-labeled glycine was used to measure the life span of erythrocytes in marmots. Studies were made at room temperature, in the cold room (4.5°C) and during hibernation. Low environmental temperature increased the life span of the erythrocytes but there appeared to be a limit to this increase which, however, did not occur in the hibernating animal.

123. Braden, A. W. H. and Austin, C. R. Fertilization and fertility in mammals. *Australian Vet. J.* 29: 129–32 (May), 1953.

The principal events which take place between mating and the 1st segmentation of the fertilized egg are discussed and an attempt is made to provide a logical concept of the mechanisms involved.

124. Budds, O. C., Russell, E. S. and Abrams, G. E. Effects of genetics and anesthesia upon granulocyte and agranulocyte levels in seven inbred mouse strains. *Proc. Soc. Exptl. Biol. Med.* 84: 176–8 (Oct.), 1953.

Mean values (Randolph's method) for granulocytes and agranulocytes in normal and anesthetized young adult mice of the following strains are reported: A/Jax, AKR/Jax, BALB/c Jax, C3H/Jax, C57BL/6 Jax, DBA/1 Jax, DBA/2 Jax. Analysis of variance demonstrated significant genetic differences among the strains in granulocyte and agranulocyte counts, with anesthesia contributing significantly to variations in granulocyte number.

125. Bush, I. E. Species differences in adrenocortical secretion. *J. Endocrinol.* 9: 95–100 (Jan.), 1953.

Adrenocortical secretion in rats, rabbits, cats, ferrets and monkeys was studied by direct analysis of sampies of adrenal venous blood, using paper chromatography. All species examined secreted large amounts of 17-hydroxycorticosterone and/or corticosterone, and some a third compound, provisionally identified as 11-hydroxyandrost-4-ene-3:17-dione. ACTH increased the secretion rate of all components of the secretion. It is suggested that the species differences observed in adrenocortical secretion are genetically determined, and cannot at present be related to any known differences of adrenocortical function in these species. Observable physiological differences may, however, be discovered, and caution should be exercised in generalizing from the results of ACTH treatment in the rat and rabbit. (From author's summary)

126. Capraro, V. A new method of measuring oxygen consumed in the metabolism of small animals. *Nature* 172: 815 (Oct. 31), 1953.

The autoregulating method is based on the principle of replacing, by means of electrolysis, the O consumed in measurements of metabolism. The metabolism chamber is described. Using the method, the average heat production of the albino mouse was found to be 30 Cal/kg/hr., and that of the albino rat 15 Cal/kg/hr. (Also in Italian: Capraro, V. and Meli, A. Un nuovo apparecchio per il metabolismo dei piccoli animali. (Apparatus for small animal metabolism studies.) *Studi Urbinati, Fac. farm.* 28: 5–11, 1954.)

127. Chao, F.-C. and Tarver, H. Breakdown of urea in the rat. *Proc. Soc. Exptl. Biol. Med.* 84: 406–9 (Nov.), 1953.

The site of urea breakdown in the intact rat is determined and its significance is assessed.

128. Christian, J. J. The relation of adrenal weight to body weight in mammals. *Science* 117: 78–80 (Jan. 23), 1953.

Adrenal and body weights were charted for 19 species of wild mammals, 3 captive species approaching wild activity, highly active guinea pigs, and man. Body weights ranged from 2.6 gm to 175 kg. The plot of the mean log of the adrenal weight against the

mean log of the body weight for each species shows a linear function, indicating that the adrenal weight is a constant power of the body weight for a wide range of species and body weight. (Author's abstract)

129. COHEN, C. AND FULLER, J. L. The inheritance of blood types in the dog. *J. Heredity* 44: 225–8 (Nov.–Dec.), 1953.

The frequency of occurrence of blood types in dogs was analyzed. The results show that according to the systems studied above, the factors appear to be inherited as simple Mendelian dominants with no evidence of linkage of multiple allelic pairs. (Author's summary)

130. DEL GRECO, F., OLMSTED, F., MASSON, G. M. C. AND CORCORAN, A. C. Graphic measurement of arterial pressure in the unanesthetized rat. *J. Lab. Clin. Med.* 41: 729–37 (May), 1953.

The method involves graphic registration of tail pulse and pressure in a proximal occluding cuff. Tracings from normal rats are given. Results of measurements by graphic and microphonic methods are compared.

131. DENTON, A. E., GERSHOFF, S. N. AND ELVEHJEM, C. A. A new method for cannulating the portal vein of dogs. *J. Biol. Chem.* 204: 731–5 (Oct.), 1953.

A method for introducing a cannula into the portal vein of dogs is described. In determining the value of obtaining samples of plasma from the portal vein after feeding experimental rations, it was found that a much greater increase in the concentration of amino acids can be detected in the portal vein than in the radial vein at various times after ingestion of a meal. (Author's summary)

132. DESCLIN, L. Action d'un éclairage continu ou de l'obscurite permanente sur la croissance des jeunes chez le rat lactant normal ou chatré. (Influence of continuous light or permanent darkness on the growth of normal lactating or castrated young rats.) *Ann. endocrinol. (Paris)* 14: 472–6, 1953.

Exposure of lactating rats to continuous light results in decreased growth of the young until the 21st day with a maximum decrease during the first 10 days. Maintenance of the mother rats in permanent darkness depresses growth of the young only during the first 10 days of life. When the mothers are castrated directly after birth, exposure to continuous light does not influence the growth of the young.

133. DOUGHERTY, T. F. AND FRANK, J. A. The quantitative and qualitative responses of blood lymphocytes to stress stimuli. *J. Lab. Clin. Med.* 42: 530–7 (Oct.), 1953.

Total leukocyte counts and absolute numbers of the various leukocytes (lymphocytes, polymorphonuclears and eosinophils) were determined in 40 normal mice.

134. DUBREUIL, R. AND TIMIRAS, P. S. Effect of cortisone on free amino acids in the serum and organs of the rabbit. *Am. J. Physiol.* 174: 20–6 (July), 1953.

Average body and organ weights of normal male white rabbits, based on analyses from four animals, are given as follows: body weight (gm) initial 1,464±30.8, final 1,421±32; organ weights gm/kg body weight, liver 34.3±2.5; kidney 6.0±1.9; heart 2.6±0.5; adrenals 0.073±0.006; thymus 2.04±0.11; spleen 0.454±0.084. The content of the individual free amino acids in serum, liver, kidney, muscle and thymus is listed.

135. DUMAS, J. *Les animaux de laboratoire: Anatomie, particularités physiologiques, hématologie, maladies naturelles, expérimentation.* (*Laboratory Animals: Anatomy, Physiologic Peculiarities, Hematology, Spontaneous Diseases, Experimentation.*) Paris, Éditions Médicales Flammarion, 1953, 719 pp.

The book contains chapters on guinea pigs, rabbits, mice, rats, other rodents such as hamster, ferret, spermophile; birds, monkeys, cats and dogs. Anatomy and physiology, housing, sanitation, nutrition and diseases are described. A section is devoted to marking, restraint, anesthesia, surgical equipment, blood collecting and injection techniques, and necropsy procedures.

136. EGGLETON, M. G. AND SHUSTER, S. Excretion of glucose by the cat's kidney. *J. Physiol. (London)* 122: 54–5P (July), 1953.

In man and dog, an increase of the blood sugar concentration produces an increase in reabsorption of the filtered glucose by the renal tube cells until a maximum value is reached. Further increase of the filtered load leaves this value unchanged. In the cat, however, the amount reabsorbed increases indefinitely with increasing load, though at a diminishing rate.

137. EISEN, A. Z., MONTAGNA, W. AND CHASE, H. B. Sulfhydryl groups in the skin of the mouse and guinea pig. *J. Natl. Cancer Inst.* 14: 341–53 (Oct.), 1953.

Sulfhydril groups were studied in the skin of normal guinea pigs and in the sole pads, the esophagus and tongue of normal mice of strain BCU white and C57BL as well as in one epithelioma from a hairless mouse. The tissues were stained with Barrnett and Seligman's method for the demonstration of protein-bound sulfhydryl groups.

138. ERSHOFF, B. H. AND GAINES, J. G. Comparative effects of total body and tail heating on the peripheral leukocyte count of the rat. *Science* 118: 20–1 (July 3), 1953.

Comparative effects of total body and tail heating on the count of red and white blood cells, lymphocytes and granulocytes of normal female rats of the Long-Evans strain, maintained on three different diets, are given.

139. EVANS, F. L. Unusual reproductive phenomena in rodents. *Science* 117: 159–60 (Feb. 13), 1953.

The delivery in rat, mouse and guinea pig of 2 successive litters by the same female without second breeding is reported. Based on personal communication, the phenomenon appears to be more common than a review of the literature indicated.

140. FARNER, D. S., MEWALDT, L. R. AND IRVING, S. D. The roles of darkness and light in the activation of avian gonads. *Science* 118: 351–2 (Sept. 25), 1953.

The photoperiodic responses of white-crowned sparrows (*Zonotrichia leucophrys gambelii*) were studied. The results suggest that the light-stimulated gonadotropic mechanism becomes active almost immediately after the start of the photoperiod and carries over after its end. The rate of testicular response would then be a direct function of the summated daily gonadotropic effects of the photo- and carry-over periods.

141. FARRELL, G. L. AND LAMUS, B. Steroids in adrenal venous blood of the dog. *Proc. Soc. Exptl. Biol. Med.* 84: 89–93 (Oct.), 1953.

Adrenal venous blood of the dog has been quantitatively analyzed by paper chromatography for steroid components. Fourteen

fractions have been isolated; three have been identified as 17-hydroxycorticosterone, corticosterone and 11-desoxy-17-hydroxy-corticosterone; seven of the unidentified fractions exhibit chemical reactions characteristic of adrenocorticosteroids. (Author's summary)

142. FIDANZA, F., KEYS, A. AND ANDERSON, J. T. Density of body fat in man and other mammals. *J. Appl. Physiol.* 6: 252–6 (Oct.), 1953.

Density values of body fats from dog, rat, rabbit, guinea pig, steer, pig, and lamb are reported. No differences were found between internal and s.c. fats of dog, rat, rabbit and guinea pig but significant differences according to location were found in the steer, pig and lamb.

143. FRIED, G. H. AND TIPTON, S. R. Comparison of respiratory enzyme levels in tissues of mammals of different sizes. *Proc. Soc. Exptl. Biol. Med.* 82: 531–2 (Mar.), 1953.

Heart, kidney, liver, and brain of the cow, rat, and mouse were assayed for maximal activity of succinoxidase and malic dehydrogenase. The levels of the two enzymes generally reflect the inverse relationship of metabolism with body size in that the tissues of the cow were lowest, those of the rat intermediate, and those of mouse highest in activity for these enzymes. Enzyme Qo_2 values (mm^3 O/mg dry weight/hr) for the tissues of cow, rat and mouse and some intraspecific differences in the enzymatic activities in mice and rats are given. (Author's summary modified)

144. FULLER, J. L. Cross-sectional and longitudinal studies of adjustive behavior in dogs. *Ann. N. Y. Acad. Sci.* 56, Art. 2: 214–24 (Feb.), 1953.

The dogs used in these experiments were kept in a large room for 16 wk. with an average daily human contact of 15 min. The mother was removed when the pups were 10 wk. old. At 16 wk. of age the dogs were placed in outside yards. The dog-dog as well as dog-man relationships were studied. Cases of sexual behavior and maladaptive behavior including fighting were analyzed. Variations of behavior were noted in different breeds. Criteria of maladjustment and scoring methods for measuring dog responses to man are presented. Breed differences in motivation tests and in heart rate during reactivity tests are tabulated. The influence of genetic factors on behavior is pointed out.

145. GALLAGHER, D. J. A. AND GRIMWOOD, L. H. A simple electrical method for measuring systolic blood pressure in the intact rat. *J. Physiol. (London)* 121: 163–6 (July), 1953.

The method described introduces a simplification of present techniques. The increase in tail volume, as blood first enters the tail when the pressure in an encircling sphygmomanometer cuff is reduced to the systolic level, is detected by a lever system which alters the resistance of an electrical circuit. In 72 Wistar rats, with equal sex distribution, from 150–250 gm weight, systolic pressures under light ether ranged from 82–140 mm Hg.

146. GEORGE, W. Some animal reactions to variations of temperature. *Endeavour* 12: 101–5 (Apr.), 1953.

The following rules apply to warm-blooded animals: large body size is directly correlated with cold climate; protruding body parts are relatively shorter in individuals in the cooler parts of the range of a species than in warmer areas; in the warm and humid parts of the range of a species individuals contain relatively more melanin. The expression of some genes can be altered by temperature. High temperature is correlated with a comparatively high mutation rate and favors a more rapid evolution than a low one.

147. GRAD, B. Changes in oxygen consumption and heart rate of rats during growth and ageing: role of the thyroid gland. *Am. J. Physiol.* 174: 481–6 (Sept.), 1953.

Oxygen consumption and heart rate were determined in male and female Wistar rats continuously from birth to old age.

148. GREEN, E. L. A skeletal difference between sublines of the C3H strain of mice. *Science* 117: 81–2 (Jan. 23), 1953.

A variance regarding skeletal type in sublines of C3H mice is pointed out; at least 2 distinct types, C3H/St or C3H/Bi for Strong's and Bittner's sublines and C3H/He for the Andervont (Heston) subline must be recognized. Possible explanations of this genetic difference are mentioned.

149. HALBERG, F. AND BOCK, F. Eosinopenia during last third of pregnancy and after delivery in several stocks of mice. *Proc. Soc. Exptl. Biol. Med.* 83: 338–40 (June), 1953.

Eosinopenia was observed during the last third of pregnancy in several stocks of mice. The mean eosinophil level of females of the Ax and the Zb stock, pregnant 2 wk. and more, was less than half of that noted in nonpregnant mice. Eosinopenia was also noted during the 48 hr. following the delivery of the young.

150. HALBERG, F., VISSCHER, M. B. AND BITTNER, J. J. Eosinophil rhythm in mice: Range of occurrence; effects of illumination, feeding and adrenalectomy. *Am. J. Physiol.* 174: 109–22 (July), 1953.

Eosinophil counts of individual mice of various strains during 2 daily periods are presented. Cyclic eosinopenia was noted in both male and female mice in the absence of stimulation other than daily routine. Among environmental factors the lighting and feeding regimen has a decided influence on the eosinophil rhythm. Adrenalectomy suppresses the eosinophil rhythm.

151. HESTON, W. E., JAY, G. E., JR., KAUNITZ, H., MORRIS, H. P., NELSON, J. B., POILEY, S. M., SLANETZ, C. A., ZUCKER, L. M., ZUCKER, T. F. AND SHILS, M. E. (Chairman). *Rat Quality. A Consideration of Heredity, Diet and Disease. Symposium, Jan. 31, 1952.* New York, Nat. Vitamin, 1953, 138 pp.

The following papers are presented: Growth criteria; natural history of chronic respiratory disease in the albino rat; development of inbred strains and their use in research; problems in breeding for quality; studies of genetic and nutritional factors which influence uniformity in laboratory animals; history and information concerning the rat colonies in the animal section of the National Institutes of Health; use of inbred strains in biological research; evaluation of commercial rat diets; experiences with semipurified diets as stock rations.

152. HOET, P. L. Sugar tolerance and pregnancy in the rabbit. *J. Physiol. (London)* 120: 68–9P (Mar.), 1953.

Figures of the glucose tolerance curve from rabbits before, on the 5th and 15th day of pregnancy and 2 days after birth are given. The tolerance is impaired during gestation but becomes normal again within 48 hr. after the end of pregnancy. Rabbits are very sensitive to the hyperglycemic effect of cortisone during pregnancy.

153. HORN, V., JAHN, U. AND WILLE, H. Das Knochenmarkzellbild im Sternalpunktat des gesunden Hundes.

(Sternal marrow biopsy and the cell picture in healthy dogs.) *Arch. exptl. Veterinärmed.* 7: 177–91, 1953.

A method for obtaining bone marrow by sternal puncture from the dog is reported and the cytology of the bone marrow is described. The myelograms and blood pictures of 20 healthy dogs are tabulated.

154. HORVATH, S. M., HUTT, B. K., SPURR, G. B. AND STEVENS, G. E. Some metabolic responses of dogs having low body temperature. *Science* 118: 100–1 (July 24), 1953.

Two dogs were anesthetized with 30 mg/kg of Nembutal and subjected to cold exposure which lowered their body temperature about ⅓ below normal. Data on the following observations are summarized in a table: rectal and mean body temperature, heart rate, calculated heat content, O consumption, heat production, respiratory rate, respiratory minute volume, total heat loss, total heat production, theoretical total heat production.

155. HORWITZ, S. A., SPANIER, M. R. AND WIGGERS, H. C. The electrocardiogram of the normal dog. *Proc. Soc. Exptl. Biol. Med.* 84: 121–5 (Oct.), 1953.

A table of values is presented for the electrocardiogram of the average normal laboratory dog; trained, unanesthetized, and in the supine position, based on data from 62 tracings on 30 dogs. Data obtained from 10 serial tracings on each of 3 dogs indicates a variation within the same animal not significantly different from that obtaining among different animals. It is recommended that to establish the normal electrocardiogram of a dog a mean of 3 tracings taken at different times be used to reduce the effect of the occasional extreme value. (Author's summary)

156. JOHANSEN, E. A system for recording oral conditions and dental lesions in the live Syrian hamster. *J. Dental Research* 32: 578–84 (Aug.), 1953.

A series of charts for the progressive recording of eruption and attrition of the dentition, of dental caries, and of the different phases of periodontal disease is described. Composites of these charts for recording the accumulation of supra- and subgingival deposits are discussed. (Author's summary)

157. JONES, D. C., KIMELDORF, D. J., RUBADEAU, D. O. AND CASTANERA, T. J. Relationships between volitional activity and age in the male rat. *Am. J. Physiol.* 172: 109–14 (Jan.), 1953.

Male Sprague-Dawley rats of 5 different ages were confined to wheel cages and their volitional activity was recorded for 7 consecutive weeks. A detailed description of the wheel cage apparatus used is presented. According to results, volitional activity is a function of age and of the animal's experience in the wheel.

158. LEBO, D. A simplified method for measuring emotional defecation in the rat. *Science* 118: 352–3 (Sept. 25), 1953.

A clean standard cage placed in an unfamiliar room was substituted for the open field test. Emotional defecation was measured by the statistical sign test.

159. PAYNE, L. C. *A Handbook of Veterinary Endocrinology.* Minneapolis, Burgess, 1953, 41 pp.

The functions of the endocrine glands (thyroid, parathyroid, pancreas, adrenal-pituitary, ovary, placenta, testicle) are described briefly. The hormones available to the clinician and their commercial sources are listed, as well as their functions, symptoms of their deficiency and excess in the body and suggested uses.

160. REYNOLDS, H. C. The opossum. *Sci. American* 188: 88–90, 92, 94 (June), 1953.

The living, feeding and breeding habits of the opossum are described.

161. WATTS, D. T. AND GOURLEY, D. R. H. A simple apparatus for determining basal metabolism of small animals in student laboratory. *Proc. Soc. Exptl. Biol. Med.* 84: 585–6 (Dec.), 1953.

The device described is economical, simple to construct and operate and quite accurate for equipment of its simplicity. Normal adult rats, 200–300 gm weight, had a mean O consumption of 8.6±0.3 l/m²/hr. After i.p. injection of 40 mg/kg of pentobarbital-Na, the O consumption was 5.6±0.2 l/m²/hr., and after administration of 5 mg/kg/day of Tapazole in the drinking water for 3 wk. it was 7.8±0.3 l/m²/hr.

162. WHITNEY, L. F. *The Complete Book of Cat Care.* New York, Doubleday, 1953, 284 pp.

A diagnostic table is presented as a help to identify the common diseases of cats. The physiology of cats, diseases and their treatment, restraint and surgery, nutrition, reproduction and heredity are discussed.

163. WYMAN, L. C., FULTON, G. P., SUDAK, F. N. AND PATTERSON, G. N. Electrocardiograms and serum electrolyte levels in hamsters with adrenal insufficiency and hypercorticalism. *Proc. Soc. Exptl. Biol. Med.* 84: 280–3 (Nov.), 1953.

Electrocardiograms were obtained by means of hypodermic electrodes, a preamplifier and a cathode ray oscilloscope. Electrolyte determinations on the blood serum were made by flame photometer. Average values for Na and K (mEq/l) and for T and P waves in the EKG are given for 24 normal hamsters.

164. ANNEGERS, J. Total body water in rats and mice. *Proc. Soc. Exptl. Biol. Med.* 87: 454–6 (Nov.), 1954.

Total body water by vacuum desiccation, total body fat by ether extraction, and fat-free dry body weight were measured in normal mice and rats, and in starved and dehydrated rats. (Condensed from author's summary)

165. BARTLETT, R. G., JR., HELMENDACH, R. H. AND INMAN, W. I. Effect of restraint on temperature regulation in the cat. *Proc. Soc. Exptl. Biol. Med.* 85: 81–3 (Jan.), 1954.

Healthy adult male and female cats were restrained in essentially normal positions by binding of legs or head to stationary supports and placed in a cold room (−15°±2°C). Their body temperature was compared with that of cats killed by an overdose of Na pentobarbital and placed in the cold and with that of controls housed individually in large cages in the cold room.

166. BECKER, E. L. AND JOSEPH, B. J. The volumes of distribution of sodium thiosulfate and inulin in normal dogs. *U. S. Air Force, School of Aviation Medicine Project No. 21-1201-0001, Rept.* No. 8, Oct., 1954.

A method for the measurement of extracellular fluid in the body compartments in normal and altered physiological states is described. The volume of distribution of inulin, as determined by the

urinary recovery method, was 16%–20% of body weight while that of thiosulfate was 20%–25%. Urinary excretion of thiosulfate during the 1st hr. after injection amounted to 53% of the dose, with a total recovery of 57% in 5 hr.

167. BERNSTEIN, L. The pressure volume diagram of the rabbit's lung *in vivo*. *J. Physiol.* (*London*) 123: 44–5P (Dec. 1953), 1954.

Pressure-volume curves have been determined in anesthetized and curarized rabbits, while under artificial respiration. When a second determination of the pressure-volume curve, up to an inflation volume of 60 cc, was made immediately following the first determination, the resulting curve had a lower slope, indicating some 'adaptive' mechanism in the lung.

168. BRISCOE, S. Cholinesterase activity of left and right atria of the rabbit's heart. *J. Physiol.* (*London*) 126: 623–6 (Dec.), 1954.

The cholinesterase activity of the left and right atria of the rabbit's heart has been determined manometrically, using specific substrates for true and pseudo-cholinesterase. True cholinesterase activity is higher in the right atrium than in the left. Pseudo-cholinesterase activity is higher in the left atrium than in the right (Author's summary)

169. BRUCE, H. M. Some common causes of infertility in laboratory animals. *J. Animal Technicians Assoc.* 4: 75–7 (Mar.), 1954.

The following factors are considered to be connected with infertility in laboratory animals: diet, disease, environmental factors such as temperature, light, noise, crowding and handling.

170. CALHOUN, M. L. *Microscopic Anatomy of the Digestive System of the Chicken*. Ames, Iowa State College Press, 1954, 108 pp.

The literature on the anatomy of the chicken is reviewed and a microscopic study of the digestive tract of the chicken at different ages is reported.

171. CHASE, H. B. Growth of the hair. *Physiol. Revs.* 34: 113–26 (Jan.), 1954.

Based on a review of 78 references, the authors point out that hair growth is a cyclic phenomenon intimately related with the structure and physiology of the skin as a whole. The following topics are discussed: development of the follicle and the first hair; phases of the cycle; experiments relating to the growth of the hair; relation of hair growth to the skin.

172. CIZEK, L. J. Total water content of laboratory animals with special reference to volume of fluid within the lumen of the gastrointestinal tract. *Am. J. Physiol.* 179: 104–10 (Oct.), 1954.

Data are presented on the magnitude of the fluid located within the gastrointestinal tract of commonly used laboratory animals (rabbits, guinea pigs, rats, dogs, mice, hamsters, goats) and its relationship to the total body water as determined by desiccation.

173. DAVIS, T. R. A. AND MAYER, J. Imperfect homeothermia in the hereditary obese-hyperglycemic syndrome of mice. *Am. J. Physiol.* 177: 222–6 (May), 1954.

Mice with a hereditary obese-hyperglycemic syndrome (obtained from the Jackson Memorial Laboratory at Bar Harbor, Maine) were shown to exhibit an extreme sensitivity to cold leading to death on exposure to temperatures normally endured by the nonobese siblings. The failure of these obese mice to raise their metabolic rate in the cold was studied.

174. DUNN, T. B. Normal and pathologic anatomy of the reticular tissue in laboratory mice, with a classification and discussion of neoplasms. *J. Natl. Cancer Inst.* 14: 1281–1433 (June), 1954.

General survey of the literature: normal mice, mice with non-neoplastic diseases, mice with neoplastic disease of the reticular system; examination of the peripheral blood and bone marrow; blood and blood-forming organs: number and morphology of particular cell types, organs of the reticular tissue; nonneoplastic alterations: functional response, aging and degenerative changes, hyperplasia of particular cell types, reactions to injury; neoplastic and related conditions; lesions found in mice of various strains and types of hybrids at the National Cancer Institute; significance of neoplastic lesions of the reticular system in mice in relation to disease in man. An extensive bibliography is included.

175. EAYRS, J. T. Spontaneous activity in the rat. *Brit. J. Animal Behaviour* 2: 25–30, 1954.

The diurnal activity of adult female rats living in stabilimeter cages was compared with their performance when housed in activity wheels. The 2 kinds of apparatus show the way in which these factors modify spontaneous activity. Apparently activity in a wheel satisfies a need which is not present when the animal is housed in a stabilimeter cage. (*Abstr. J. Animal Technicians Assoc.* 6: 27 (June), 1955.)

176. EYQUEM, A. AND PODLIACHOUK, L. Les groupes sanguins des chats. (The blood groups of cats.) *Ann. inst. Pasteur* 87: 91–4 (July), 1954.

In a serologic study with adult normal cats 85% of the tested animals were found to have blood type containing antigen A and 15% blood type containing antigen B. About 15% of the cats possessed an isoagglutinin. All the blood types containing anti-A isoagglutinins had an identical specificity.

177. FEKETE, E. Gain in weight of pregnant mice in relation to litter size. *J. Heredity* 45: 88–9 (Mar.–Apr.), 1954.

Data on the gain in weight during pregnancy of 57 C57BL/6 mice gravid with litters varying in size from 1–10 are presented in a diagram.

178. FINDLAY, J. D. AND BEAKLEY, W. R. Environmental physiology of farm mammals. In: HAMMOND, J. ed. *Progress in the Physiology of Farm Animals*. London, Butterworth & Co., 1954, pp. 252–98.

A review with many references.

179. GINSBURG, B. E. AND FULLER, J. L. A comparison of chemical and mechanical alterations of seizure patterns in mice. *J. Comp. and Physiol. Psychol.* 47: 344–8 (Aug.), 1954.

Genetically homogeneous mice of the DBA/1 strain, produced by over 100 generations of brother × sister matings, are known to be approximately 60% susceptible to seizures during the age period from 30–45 days when subjected for 1.5 min. to noise caused by doorbells at intensities of 86–104 decibel. A complete record of behavior may be made during each test. The exposure technique (noise) used is described in detail.

180. GOLDIE, H., JONES, A. M., RYAN, H. AND SIMPSON, M. Leukocyte counts in the blood from the tail and the heart of the mouse. *Science* 119: 353–4 (Mar. 12), 1954.

Leukocyte counts in blood specimens taken from various areas of the vascular system of the same mouse have shown that the leukocyte concentration decreased progressively during passage of the blood from tail capillaries, through the femoral vein and right heart, to the left heart. The counts were equalized by treatment of the mice with total body heating, ether or anticoagulants.

181. GRÜNEBERG, H. Variation within inbred strains of mice. *Nature* 173: 674–6 (Apr. 10), 1954.

Based on literature references, evidence is presented that inbred strains of mice are sometimes more variable than genetically mixed populations. Percentage incidence of 11 skeletal variants for 3 inbred strains (C57BL/Gr, CBA/Gr) and 2 groups of sublines of C57BL/Gr are listed. The genetic background of these variants is multifactorial with environment and diet playing an important role. In the case of antigenic characters, however, the reaction of pure-line mice is much more uniform than that of a genetically mixed batch of mice. Thus, while purebred mice are superior material for certain types of experiments, they may be inferior to genetically mixed ones for other purposes.

182. HALBERG, F. AND VISSCHER, M. B. Temperature rhythms in blind mice. *Federation Proc.* 13: Abstr. No. 214 (Mar.), 1954.

Rhythms in rectal temperature were studied for 200-day periods on blinded and on sham-operated male CBC and DBA mice, kept on a regimen providing for 12 hr. of light alternating with 12 hr. of darkness. A slight but clear shortening of cycle length was noted after blinding. The results obtained are supported by data on congenitally anophthalmic ZRD mice.

183. HALBERG, F., ZANDER, H. A., HOUGLUM, M. W. AND MÜHLEMANN, H. R. Daily variations in tissue mitoses, blood eosinophils and rectal temperatures of rats. *Am. J. Physiol.* 177: 361–6 (June), 1954.

The daily rhythm was studied in tissue mitoses, blood eosinophils and rectal temperatures of male Line-3 black rats under standardized conditions of environment and sampling schedule. Rectal temperature showed a nocturnal high followed by a diurnal low; the eosinophil level was lower at night than in the morning; the mitotic rates varied with the tissue.

184. HAMILTON, L. H. AND HORVATH, S. M. Comparison of blood cell counts from major vessels in the dog. *Proc. Soc. Exptl. Biol. Med.* 86: 360–3 (June), 1954.

Blood cell counts were compared in samples drawn simultaneously from the aorta, right ventricle, superior vena cava, caudal vena cava, hepatic vein, and/or peripheral veins in dogs. The study was done on normal and splenectomized dogs, either unanesthetized or anesthetized with pentobarbital. No differences in erythrocyte or leukocyte distributions were demonstrated as a result of anesthetization or splenectomy. The erythrocyte and leukocyte counts were the same in arterial and venous blood samples and in venous samples from different major vessels. The method of catheterizing the blood vessels is described. (Condensed from author's summary)

185. HAMMOND, J., ed. *Progress in the Physiology of Farm Animals.* London, Butterworth & Co., 1954, Vols. I, II and III, 1043 pp.

Vol. I covers nutrition, metabolism and environment of fowl and domestic animals. Vol. II concerns growth, animal behavior, locomotion and reproduction (fowl). Vol. III continues the section on reproduction in animals and milk production.

186. HARDWICK, D. C. Age changes in the histamine content of rat skin. *J. Physiol. (London)* 124: 157–65 (Apr.), 1954.

The histamine content of the skin in a pure, inbred strain of Wistar WAG rats was determined from birth to 514 days of age. The histamine content of the rat skin in large and small litters and the effect of weaning procedures on the histamine content was also studied.

187. HARRIS, R. S., HERDAN, G., ANCILL, R. J. AND YOFFEY, J. M. A quantitative comparison of the nucleated cells in the right and left humeral bone marrow of the guinea pig. *Blood* 9: 374–8 (Apr.), 1954.

In 17 young male guinea pigs a quantitative study was made of the nucleated cells (erythroid, myeloid, lymphocytes, monocytes) of the bone marrow in the right and left humerus. Analysis of the data shows a close correspondence between the 2 sides in regard to the main cell groups. (Author's summary)

188. HENSCHEL, J. Versuche über den Wasserhaushalt von Haus- und Wanderratten. (The water metabolism of house rats and migratory rats.) *Z. angew. Zool.* 1954: 243–59.

The drinking water consumed and the urine eliminated was determined in house rats and migratory rats.

189. JOFFE, M. H. A method of assessing experimental pulmonary edema. *Science* 120: 612–13 (Oct. 15), 1954.

A method is described for the calculation of lung weight, whereby each animal provides its own control value; this greatly reduces the number of animals necessary per experiment. The body and lung weights of untreated guinea pigs and those treated percutaneously with phosgene oxime are tabulated.

190. MCLAREN, A. AND MICHIE, D. Factors affecting vertebral variation in mice. I. Variation within an inbred strain. *J. Embryol. Exptl. Morphol.* 2, Pt. 2: 149–60 (June), 1954.

By means of x-ray photography the number of lumbar vertebrae was counted in samples of mice from 11 colonies of the C3H inbred strain. The new data have revealed 3 factors with significant effects on vertebral variation within substrains of C3H strain: *1*) A fluctuating variable of the mother's physiology which affects the prenatal development of the offspring. *2*) A difference between the sexes; the percentage of mice with 5 lumbar vertebrae is higher among males than among females. *3*) Divergences between colonies of the same substrain. The available data are not competent to distinguish the relative contributions to these divergences of nature and nurture. (Condensed from author's summary)

191. MARTINEZ, C., GRANDE, F. AND BITTNER, J. J. Alloxan diabetes in different strains of mice. *Proc. Soc. Exptl. Biol. Med.* 87: 236–7 (Oct.), 1954.

Male mice of the C_3H, C, A and D_8 strains are susceptible to the diabetogenic action of alloxan. A difference in susceptibility depended upon the strain, the D_8 was the most susceptible and the C_3H, the most resistant, to a given amount of alloxan injected. Glucose tolerance tests in diabetic as well as in nondiabetic mice are presented. (Condensed from author's summary)

192. MICHAELSON, I. C. *Retinal Circulation in Man and Animals.* Springfield, Ill., C. C. Thomas, 1954, 146 pp.

XUM

The developmental and adult condition of the blood vessels of the inner eye of the vertebrates is reviewed and the role of these vessels in the nutrition of the retina is discussed. A detailed description of the vascular conditions of eel, roach, frog, pigeon, horse, rabbit, cat, rat and man is given.

193. Nay, T. and Fraser, A. S. Growth of the mouse coat. III. Patterns of hair growth. *Australian J. Biol. Sci.* 7: 361–7 (Feb.), 1954.

Hair growth cycles were observed for a period of 60 days in naked mice of different ages. The duration of the total hair cycle varied according to position and increased from head to tail. Within each position over all ages the duration was constant. These facts explain the pattern of growth cycles in naked mice. (Author's summary)

194. Ruegamer, W. R., Bernstein, L. and Benjamin, J. D. Growth, food utilization, and thyroid activity in the albino rat as a function of extra handling. *Science* 120: 184–5 (July 30), 1954.

Weanling male albino rats of the Denver University strain or Sprague-Dawley weanling rats were used. Extrahandled rats, that is animals which were individually petted for 10 min/day, showed better growth and utilization of food than the unhandled ones and exhibited also more activity and curiosity. Increased thyroid activity was noted in the unhandled groups.

195. Squibb, R. L., Guzman, M. A., and Scrimshaw, N. S. Effect of high environmental temperatures on metabolism. I. Growth and blood constituents of rats exposed to 94°F. for 72 hours. *J. Nutrition* 52: 155–63 (Feb. 10), 1954.

White male rats weighing 225–285 gm each (3rd-generation progeny of stock from the Bureau of Animal Industry, U.S. Department of Agriculture) were kept at 94°F and 50%–75% humidity for 72 hr., controls at 76°F and 35%–75% humidity. One set of each group was given feed ad libitum while the other set was on a restricted (5 gm) food intake. The response of the animals in terms of mortality rate, feed consumption, growth and serum levels of protein, riboflavin, carotene, vitamin A, ascorbic acid, alkaline phosphatase and P was recorded. Heat-treated rats at ad libitum feeding consumed less than controls, lost weight and had depressed levels of riboflavin, vitamin A, ascorbic acid and alkline phosphatase while total proteins were increased. At restricted feeding all lost weight but only the heat-treated ones showed depressed levels of vitamin A and ascorbic acid.

196. Thompson, W. R. and Heron, W. The effects of early restriction on activity in dogs. *J. Comp. and Physiol. Psychol.* 47: 77–82 (Feb.), 1954.

Restriction, of 3 degrees of severity, was imposed on 12 Scottish terriers for the 1st 7–10 mo. of life. The results of these experiments justify the following conclusions: Exploratory activity in dogs declines as a function of time of exposure to the situation. Restricted dogs explore significantly more than normal animals. Severely restricted dogs tend to explore more than slightly restricted animals. Younger dogs explore significantly more than older animals. In testing conditions in which the mean activity of all dogs is raised significantly, the above differences do not hold. (Condensed from author's summary)

197. Weininger, O. Physiological damage under emotional stress as a function of early experience. *Science* 119: 285–6 (Feb. 26), 1954.

Male albino rats of pure Wistar strain when gentled 10 min/day for 3 wk., following weaning achieved a significantly greater mean body weight and had higher rectal temperatures (suggesting altered basal metabolism) than ungentled controls. In open field trials gentled rats proved less fearful and ventured closer to a brilliantly lighted center. After exposure to stress the gentled animals at autopsy showed less damage of the cardiovascular and gastrointestinal system than the ungentled rats, as well as lower weights of adrenal gland, indicating decreased ACTH output from pituitary in response to stress.

198. Afonsky, D. Blood picture in normal dogs. *Am. J. Physiol.* 180: 456–62 (Mar.), 1955.

Data on hemoglobin concentration, red and white cell counts, hematocrit values and indices for 30 control dogs are tabulated. The techniques used are described.

199. Babineau, L.-M. and Pagé, E. On body fat and body water in rats. *Can. J. Biochem. and Physiol.* 33: 970–9 (Nov.), 1955.

Under the experimental conditions used, water represented 72% of the fat-free body mass of adult male albino rats of the Wistar strain. This constant was independent of the magnitude of the fat depots. In physiologically normal rats the nonfat dry matter can be predicted from total body water. Adaptation to cold had no effect on the water:dry matter relationships.

200. Beidler, L. M., Fishman, I. Y. and Hardiman, C. W. Species differences in taste responses. *Am. J. Physiol.* 181: 235–9 (May), 1955.

Differences in response to a chemical stimulus occur from one species to another. The electrical responses of the chorda tympani nerve to chemical stimulation of the tongue were recorded in rats, guinea pigs, rabbits, cats, dogs, hamsters and raccoons. The spontaneous activity observed during a water rinse is small in the guinea pig, hamster, and dog; moderate in the cat; and large in the rabbit. This activity in the rabbit can be suppressed with low concentrations of NaCl. The rodents respond well to NaCl compared to KCl whereas the opposite is true with the carnivores. Animals of both orders respond well to NH_4Cl. The hamster and guinea pig are easily stimulated with sucrose whereas the cat is not. (Author's summary, modified)

201. Berman, H. J., Lutz, B. R. and Fulton, G. P. Indirect method for measuring blood pressure of the hamster. *Federation Proc.* 14: Abstr. No. 35 (Mar.), 1955.

The systolic blood pressure in the arterial vessels of the hamster cheek pouch was measured by applying a cuff across the proximal portion of the pouch. The arithmetic mean and standard deviation for 52 normal hamsters, 8–12 wk. old, were found as 90±11 mm Hg. In 14 hamsters the arithmetic mean of the difference between mean pressure measured in the carotid by cannulation and in a cheek pouch artery by the cuff was 26.1 mm Hg.

202. Chen, P. S., Jr. and Neuman, W. F. Renal excretion of calcium by the dog. *Am. J. Physiol.* 180: 623–31 (Mar.), 1955.

The technique of rapid ultrafiltration of serum in a centrifuge-type apparatus and the flame photometric determination of Ca by a sensitive and direct micromethod are described. Normal renal Ca clearances were determined in 8 unanesthetized dogs while the animals were loosely restrained in the supine position on an animal board.

203. Christian, J. J. The effect of population size on the weights of the reproductive organs of white mice. *Am. J. Physiol.* 181: 477–80 (Mar.), 1955.

Male white mice caged in groups of 4, 8, 16, and 32, when killed following 3 wk. of isolation, showed an inverse relationship between population size and weight of preputial glands and seminal vesicles. The adrenal glands increased in weight through populations of 1–16/cage but declined for colonies of 32. Body and testicular weight decreased with increased population size. The increased adrenal weight and decreased body weight and weight of reproductive organs were attributed to stress produced by increasing population pressures. The cages used measured 10 × 14¼ × 6½ inches.

204. CHRISTIAN, J. J. Effect of population size on the adrenal glands and reproductive organs of male mice in populations of fixed size. *Am. J. Physiol.* 182: 292–300 (Aug.), 1955.

Increases in adrenal weight were produced in albino and wild male house mice in confined populations of fixed size, and within a limited range adrenal weight was proportional to the population density. The nature of the population pressures producing stress are unknown. The rate and magnitude of adrenal weight change in response to population density was greater in the wild than in the albino mice. The sizes of the thymus and preputial glands, seminal vesicles, and testes were inversely related to population size. The reproductive changes were attributed to suppression of gonadotrophic function with increased adrenocorticotrophic function of the anterior pituitary with a resultant decline in androgen output and testicular activity. The decline in thymus weight was attributed to adrenocortical activity. (Condensed from author's summary)

205. COHEN, C. Blood group factors in the rabbit. II The inheritance of six factors. *Genetics* 40: 770–80 (Nov.), 1955.

The inheritance of 6 blood group factors in the rabbit was studied. A system of nomenclature is proposed which is compatible with existing genetic usage and blood group terminology. (Condensed from author's summary)

206. CRISCUOLO, D. AND CLARK, R. T., JR. The myoglobin content of various rat tissues as affected by altitude and exercise. *U.S. Air Force, School of Aviation Medicine Rept.* 55–84, Dec., 1955, 11 pp.

Rats chronically exposed to 20,000 ft. simulated altitude showed an increase in myoblobin content of the heart, diaphragm, and gastrocnemius muscles. Exercise did not materially affect this increase. The increase was noted early in the period of acclimatization, about the 4th and 5th wk.; then the values returned to normal at the end of the 10th week. Rats reared at altitude showed about the same myoglobin content as the chronically exposed rats at the 10th week. (Author's summary)

207. CROFT, P. G. Biochemistry of the cerebro-spinal fluid of the dog. *Vet. Record* 67: 872–6 (Nov. 19), 1955.

Values for the common chemical and cytological constituents of cerebrospinal fluid of 25 normal dogs are given. These values are compared with those in a group of 17 dogs suffering from lesions of the nervous system. Cerebrospinal fluid studies were also made on a group of 22 dogs hyperimmunized against distemper. The diagnostic significance of the changes is discussed. A method for obtaining cerebrospinal fluid from dogs is described. (Author's summary modified)

208. DICKIE, M. M. Alopecia, a dominant mutation in the house mouse. *J. Heredity* 46: 31–4 (Jan.–Feb.), 1955.

A new mutation named alopecia which affects the formation of a normal coat of hair in mice is described. The alopecia mice regularly lose all but the guard hairs at each molt. The character seems to be semidominant since heterozygous and homozygous animals can be distinguished. (Condensed from author's summary)

209. FRAZER, J. F. D. Vaginal blood during pregnancy in the rat. *J. Physiol.* (*London*) 129: 26–7P (May), 1955.

Examination of large numbers of pregnant rats did not produce sufficient evidence to state that blood in the vagina always indicates fetal loss although fetal loss is very frequently attended by vaginal blood.

210. FRIEDMAN, J. J. Organ plasma volume of normal unanesthetized mice. *Proc. Soc. Exptl. Biol. Med.* 88: 323–5 (Mar.), 1955.

A method for the determination of the plasma volume of various mouse organs without the use of anesthesia is described. CF-1 male albino mice were injected with radioiodinated albumin and the tissue samples were assayed for radioactivity. Values are presented for plasma volume of liver, kidney, spleen, lung, intestine, skin, and muscle.

211. GOSSELIN, R. E., GABOUREL, J. D., KALSER, S. C. AND WILLS, J. H. Carbon and water contents of mouse and rat tissues. *Proc. Soc. Exptl. Biol. Med.* 90: 533–5 (Nov.), 1955.

Soft-tissue concentrations of organic carbon and of water were measured in male rats and mice. Both the method and results are thought to be useful to the radiocarbon biochemist. (Author's summary)

212. GRAVES, J. AND HIMWICH, H. E. Age and the water content of rabbit brain parts. *Am. J. Physiol.* 180: 205–8 (Jan.), 1955.

The water content of whole brain and 4 parts thereof was determined using 200 rabbits from the 17-day-old fetus to the age of 4 years. (Condensed from author's summary)

213. GRÜNEBERG, H. Genetical aspects of the breeding of laboratory animals. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 3: 29–35, 1955.

Variances of 21 characters of skeleton and teeth in the inbred mouse strains CBA and C57BL and in crosses between them are recorded. The data show that inbred strains are not interchangeable or uniformly uniform.

214. HANNA, C. H. AND MARSHALL, L. H. Effect of sampling on erythrocyte, dye and protein concentrations of venous blood of dogs. *Am. J. Physiol.* 182: 331–6 (Aug.) 1955.

The change in hematocrit values of successive blood samples was studied in normal and splenectomized dogs under various conditions. The results showed that the hematocrit decrease occurring after initial samplings was influenced by the activity of the animal prior to sampling, the presence of the spleen and some phase of the venipuncture. When all these factors were controlled, there was no significant change; when only one factor was controlled, the magnitude of the decrease was reduced. Dye and protein concentration changes were not as great as the red cell changes.

215. HARTMAN, F. A., BROWNELL, K. A. AND LIU, T. Y. Blood flow through the dog adrenal. *Am. J. Physiol.* 180: 375–7 (Feb.), 1955.

The blood flow from the left adrenal was determined by direct cannulation in 62 dogs anesthetized with Nembutal. A significant

difference in rate of flow on the basis of body weight was found between the 5–10-kg and 10–15-kg groups the latter being smaller. Dogs nearly the same weight showed great range in rate of adrenal blood flow. Differences in blood pressure between different dogs did not explain the wide difference in rate of blood flow. (Condensed from author's summary)

216. Hess, A. The nuclear topography and architectonics of the thalamus of the guinea pig. *J. Comp. Neurol.* 103: 385–419 (Dec.), 1955.

The thalamus of the guinea pig has been studied by preparing serial transverse paraffin sections of the brain stained by toluidine blue, Bodian, and myelin stains. Collections of nerve cells have been divided topographically into several nuclear groups with subdivisions into individual nuclei. The disposition and relative density and size of the nerve cells comprising each nucleus are described.

217. Ingle, D. J., Morley, E. H. and Stetten, D., Jr. Metabolism of glucose in resting and working rats. *Am. J. Physiol.* 182: 263–8 (Aug.), 1955.

C^{14} glucose was administered by continuous i.v. infusion to young adult male Sprague-Dawley rats. Urinary glucose, O_2 consumption, liver glycogen, expired $C^{14}O_2$ were compared in nonworking rats and rats subjected to faradic stimulation of either one or both hind legs. All techniques used are described.

218. Johnson, V. L. and Dunlap, J. S. Electrophoretic separation of hemoglobins from the chicken. *Science* 122: 1186 (Dec. 16), 1955.

Electrophoretic patterns were obtained from hemoglobin samples of embryos and adults of White-Olympian × New Hampshire cross chickens. Two hemoglobins were observed in each age group tested; percentage composition appeared to vary with age. As early as the 13th day of incubation 2 hemoglobins were present.

219. Johnston, C. D. and Hazleton, L. W. Normal blood cholinesterase activity in several animal species, including domestic fowls. *Federation Proc.* 14: Abstr. No. 1147 (Mar.), 1955.

The following mean normal values of cholinesterase activity (μl/ml blood or plasma/min) were obtained: cow 44.8; calf 39.3; dog (RBC) 12.7, dog (plasma) 36.9; rat (RBC) 8.5, rat (plasma) 45.6; duck 22.8; goose 13.1; turkey 41.2; cat (plasma, BuCh) 37.2.

220. Russell, E. S. Significance of the physiological pattern of animal strains in biological research. *Proc. Animal Care Panel, 4th Ann. Meeting, Chicago, Dec. 2–3, 1953*, pp. 140–50; *Brit. Med. J.* 1: 826–29 (Apr. 2), 1955.

Literature examples are cited to illustrate the genetic influence upon physiological characteristics and to show that the use of inbred animals is essential to most types of animal research. On the other hand, genetic variety between strains provides an array of valuable tools for particular types of physiological experiments. (26 references)

221. Aebi, H. and Ebnöter, P. Beitrag zur vergleichenden Biochemie der Leber. (Comparative biochemistry of the liver.) *Biochem. Z.* 328, No. 2: 126–37, 1956.

In order to determine the relationship of the metabolism of the liver to body size and species, a comparison was made of O_2 consumption of liver slices, basal metabolism, cytochrome *c*, cytochrome oxidase, pyruvate oxidation, succinic dehydrogenase concentrations in mitochondria and size of mitochondria fractions of mice, golden hamsters, rats, guinea pigs, rabbits, sheep, cattle and horses. The relative weight of the liver to body weight, and water content of liver are given.

222. Ancill, R. J. The blood volume of the normal guinea pig. *J. Physiol. (London)* 132: 469–75 (June), 1956.

The literature on the blood volume of the guinea pig is reviewed. A method for the determination of the blood volume of the guinea pig, based on the estimation of T-1824 in whole hemolyzed blood, is presented. Determination of the blood volume in 18 normal male guinea pigs gave a mean value of 7.20 ml/100 gm body weight. The figures obtained by the T-1824 dye method are compared with results of the I^{131}-labeled globulin and the vital red dye method.

223. Balmain, J. H., Biggers, J. D. and Claringbold, P. J. Glycogen, wet weight, and dry weight changes in the vagina of the mouse. *Australian J. Biol. Sci.* 9: 147–58 (Feb.), 1956.

Wet weight, dry weight and glycogen content of the vagina of the mouse at various stages of the estrous cycle, their means and fiducial limits are tabulated.

224. Bartlett, R. G., Jr. and Miller, M. A. The adrenal cortex in restraint hypothermia and in adaptation to the stress of restraint. *J. Endocrinol.* 14: 181–7 (Oct.), 1956.

Seventy adult Sprague-Dawley rats, subdivided into 5 groups, were *1*) restrained in the cold, *2*) exposed to cold without restraint, *3*) restrained at room temperature, *4*) restrained following 1 wk. adaptation, *5*) left untreated as controls, and the effect on adrenal cholesterol and ascorbic acid was determined. The effect of cortisone injection on the ability of the rat to maintain body temperature while restrained in the cold was studied.

225. Bastian, J. W. and Hill, R. Direct measurement of blood pressure in the unanesthetized rat and the effect of drugs. *J. Pharmacol. Exptl. Therap.* 116: 5 (Abstr.) (Jan.), 1956.

A method has been devised for recording blood pressure, permitting an uninterrupted observation up to 30 hours. Normal mean values for the rat were found around 126 mm Hg. A technique for intracarotid injection has been worked out whereby the drug is injected via the carotid cannula without handling the animal.

226. Bauer, F. J. Genetic and experiential factors affecting social reactions in male mice. *J. Comp. and Physiol. Psychol.* 49: 359–64 (Aug.), 1956.

One purpose of this experiment was to determine what forms of social interaction would differentiate groups of male mice differing genetically and experientially; another purpose was to determine what forms of nonadaptive or "displacement" activity would occur under conflict conditions in the test situation. (Condensed from author's summary)

227. Beatty, R. A. Relation between genetic constitution of an offspring and weight of its litter-mates. *Nature* 178: 48–9 (July 7), 1956.

When rabbit does from a single stock were artificially inseminated with semen either from a large buck of the same stock or a small one from a different strain, the offspring from the large buck averaged at birth 2.7 gm heavier than that of the small buck. The offspring of these animals, after insemination with mixed semen, showed an increased birth weight of 6.1 gm. This increase is called the "enhancement effect" in relative birth weight. Other "enhancement effects" may be produced by application of the mixed

semen technique. An enhancement effect was also demonstrated in dizygotic twin births of sheep.

228. Becker, E. L. and Joseph, B. J. Renal hemodynamics and the urinary concentrating mechanism in polycythemic dogs. *U.S. Air Force, School of Aviation Medicine Rept.* 55–140, July, 1956.

Three mongrel dogs were rendered polycythermic by exposure to a simulated altitude of 20,000 ft. for 2 years. Observations of the renal functions were made consequently with the animals at sea level.

229. Carpenter, P. L. *Immunology and Serology.* Philadelphia, Saunders, 1956, 351 pp.

The book contains the following chapters: Infection and immunity; immune reactions; antigens; serum proteins; production of antibody; antigen-antibody reaction; precipitation; agglutination; isohemagglutination; toxins and antitoxins; phagocytosis; cytolysis and complement fixation; antiviral immunity; allergy; experiments in serology (appendix). On page 234 a table lists the effect of source of complement (guinea pig, rabbit, rat, hen, goat, pigeon, horse) on hemolysis of beef erythrocytes sensitized by rabbit or goose immune serums; on page 238 titers of the components of complement in the serum of guinea pigs, men, hamsters, swine, rabbits, rats, mice, horses, beef, sheep and deer are given. In the appendix inoculation and bleeding of animals and mouse protection tests, etc., are described.

230. Caster, W. O., Poncelet, J., Simon, A. B. and Armstrong, W. D. Tissue weights of the rat. I. Normal values determined by dissection and chemical methods. *Proc. Soc. Exptl. Biol. Med.* 91: 122–6 (Jan.), 1956.

The weights of the following tissues were determined in some 300 normal male white rats (Holtzman Co., Madison, Wis.) on the basis of 2000–3000 samples: G.I. content, depot fat, muscle, supportive tissue, skin, liver, lung, heart, kidneys, testes, spleen, brain, stomach, small intestine, large intestine, thymus, blood. Components of the supportive tissue in a rat, 338 gm weight, and the weight of muscle groups as per cent of total muscle mass are also given.

231. Charles, M. S. and Fuller, J. L. Developmental study of the electroencephalogram of the dog. *Electroencephalog. and Clin. Neurophysiol.* 8: 645–52 (Nov.), 1956.

The normal developmental pattern of the EEG of the dog, from birth to an age at which a mature type of record is obtained, was studied. The method is described in detail.

232. Cohen, C. The study of blood group factors in the rabbit as an approach to some problems relating to human blood groups and transfusion. *Proc. Intern. Soc. Blood Transfusion, 6th Congr. Sept. 3–5, (Bibliotheca Haematol.* No. 7), 1956, pp. 165–70.

The use of the rabbit for isoimmunization studies is demonstrated. Eight blood group antigens varying in strength from strong to intermediate to weak were identified in the rabbit.

233. Conrad, M. C. and Miller, A. T., Jr. Age changes in body size, body composition and basal metabolism. *Am. J. Physiol.* 186: 207–10 (Aug.), 1956.

The interrelations of body weight (total and of liver, brain, heart, kidney), body composition (water, intra- and extracellular; nitrogen; protein; ash; fat) and basal metabolism were studied in 69 Sprague-Dawley albino rats ranging in age from 18 to 174 days.

234. DePugh, R. B. Growth and development. *J. Canine Genet.* (Sept.), 1956, pp. 7–31.

A general discussion.

235. Dikshit, P. K. and Taskar, A. D. Role of mammary glands on weight of suckling rats. *Proc. Soc. Exptl. Biol. Med.* 93: 235–7 (Nov.), 1956.

The 14th day weight of rats depends upon the number of "milking" glands of the mother rats. The average 14th day weight of young born in the 1st litter was lowest when compared with the weights at corresponding periods of those delivered in the subsequent litters. The average number of "functional" mammary glands of mothers nursing their 1st born was also the lowest as compared with those of mothers' rearing their 2nd, 3rd and 4th litters. (From author's summary)

236. Doggett, V. C. Periodicity in the fecundity of male rabbits. *Am. J. Physiol.* 187: 445–50 (Dec.), 1956.

Semen specimens were collected daily from 13 rabbits for prolonged periods during the course of 13 months. Total sperm count rose to a definite peak every 2–7 days (av. = 3.16 days) and then decreased again to values of from 70% to less than 1% (usually about 50%) of the preceding peak. In mature animals, the frequency of peaks was significantly different from the random distribution and significantly similar among individual animals. Intervals between peaks varied with the age of the animal.

237. Eayrs, J. T. and Baddeley, R. M. Neural pathways in lactation. *J. Anat.* 90: 161–71 (Apr.), 1956.

Studies with inbred "Birmingham" rats showed that lactation, as measured by the growth of the litter, is impaired by exposing the spinal cord or by cutting the dorsal columns. It is also impaired by lesions in this region or by cutting the dorsal roots of the nerves supplying the region of the suckled nipples.

238. Folk, G. E., Jr. and Farrand, R. L. Characteristics of hibernation of the golden hamster. *J. Animal Technicians Assoc.* 7: 14–6 (June), 1956.

Hamsters of 3 strains were exposed to cold (6°±2°C) for 4 mo. of the year; light was regulated to give 8 hr. of light/day during 9 mo. and 12 hr/day during the 3 summer months. In this experiment 45% of the animals did not hibernate. The duration of exposure to cold before hibernation was very variable ranging from 3 to 66 days. The periods of dormancy also varied widely, the mean duration of dormancy being 2.2 days and the period of activity between dormant periods about 12 hr. Hibernation appeared to act as a stress; 65% of the animals in hibernation died compared with 39% of those which did not hibernate.

239. Gaspar, S. N. Investigation of the physiologically different glycogen fractions in the rabbit. I. Comparison of the newborn and the adults. *Acta Vet. Acad. Sci. Hung.* 6: 401–9, 1956.

All examined muscular tissues of the newborn rabbit (heart muscle, m. long. dorsi, m. abdominis) are characterized by a glycogen level much above that of the adults. The percentage of the free and protein-bound glycogen is identical in the different experimental groups. The striated muscle tissues of the newborn contain the same amount of residual glycogen. A similar level is found in the white muscle of the adults, while in the red muscle it decreases to half the initial value in the course of development. The glycogen content of the liver is always lower in the newborn than in adults. The lung shows 4 times higher values than those found in adults. (Condensed from author's summary)

XUM

240. GEIGER, E. AND PINSKY, J. J. Effect of changes in environmental temperature on stomach emptying in rats. *Proc. Soc. Exptl. Biol. Med.* 91: 107–10 (Jan.), 1956.

Transfer of rats from room (22°C) to either low (3°C) or high (37°C) environmental temperature immediately following a protein meal delays emptying of stomach. After adaptation to changed surrounding temperature, stomach emptying was found to be again similar to that observed at room temperature.

241. GOLDZVEIG, S. A. AND SMITH, A. U. The fertility of male rats after moderate and after severe hypothermia. *J. Endocrinol.* 14: 40–53 (Aug.), 1956.

Male rats which had been exposed to a combination of hypoxia, hypercapnia and cold, and in which body temperature had fallen to 15°–20°C, had reduced sex drive and fertility during the subsequent 1–2 wk. When further cooled, until respiration and circulation had been arrested for 1 hr., and until the body temperature was 0°–1.5°C, they showed reduced sex drive and fertility for 8 wk. after reanimation. In rats exposed to severe hypothermia, developing spermatozoa and spermatids were damaged while the spermatogonia and spermatocytes in the seminiferous tubules were mostly unharmed. During the 1st wk. after cooling a high proportion of the epididymal spermatozoa became decapitated; their acrosomes were distorted and their midpieces and tail sheaths disrupted. (Author's summary modified)

242. GRAHAM, R. G., ALLEN, J. D., DOBSON, H. L. AND FAHLBERG, W. J. Total serum glycoprotein levels in normal New Zealand white rabbits. *Proc. Soc. Exptl. Biol. Med.* 93: 221–2 (Nov.), 1956.

The normal serum levels of glycoproteins in 19 New Zealand white rabbits are reported. It was shown that there was no significant difference between the sexes and essentially little effect on total serum glycoprotein concentration when the rabbits were bled weekly in the quantity reported over an 11-wk. period. (Author's summary)

243. GREENWALD, G. S. Sperm transport in the reproductive tract of the female rabbit. *Science* 124: 586 (Sept. 28), 1956.

Experiments with mature New Zealand giant white rabbits, which were bred once to males of proved fertility, indicated that sufficient sperm was in the tubes of every animal by 5 hr. post coitum to fertilize all viable eggs.

244. GROSVENOR, C. E. AND TURNER, C. W. Ergotamine, oxytocin and milk let-down in lactating rat. *Proc. Soc. Exptl. Biol. Med.* 93: 466–8 (Dec.), 1956.

The amount of milk let down by lactating albino rats was determined by measuring the amount of milk present in the stomachs of their young. The average weights of milk secured in 20 min. by litters are tabulated for controls, for rats treated with ergotamine before nursing and for animals given oxytocin before or after ergotamine. Administration of ergotamine decreased significantly the quantity of milk obtained by the offspring. Treatment with oxytocin before or after ergotamine restored the normal output.

245. GRÜNEBERG, H. An annotated catalogue of the mutant genes of the house mouse. *Med. Research Council (Brit.), Mem.* No. 33. London, H. M. Stationery Off., 1956, 28 pp.

The catalogue contains a classified list of the main mutant genes of the house mouse, annotations and references. It does not include genes determining antigenic differences. The laboratories which maintain the various mutant genes listed, can be located through the "Mouse News Letter."

246. HAENEL, H. AND MÜLLER-BEUTHOW, W. Vergleichende quantitative Untersuchungen über Keimzahlen in den Faeces des Menschen und einiger Wirbeltiere. (Comparative quantitative study of microorganisms in the feces of human beings and some vertebrates.) *Zentr. Bakteriol. Parasitenk. Abt. I. Orig.* 167: 123–33, 1956.

Examinations of the fecal flora of man, guinea pig, rat, horse, hen, cow, dog and rabbit for the proportion of anaerobes, aerobes, lactobacilli, coli-group organisms, enterococci, staphylococci, fungi, spores and proteus demonstrable by means of selective media, revealed that some animal species had certain types of intestinal flora in common. Man, rat, hen and dog had comparable proportions of aerobes, anaerobes, lactobacilli, coli-group organisms and enterococci. Only in the dog were staphylococci scarcely if ever demonstrable. Fungi were more frequent in the rat than in other species. The guinea pig, horse and rabbit had comparable counts of anaerobes and lactobacilli, whereas the horse had a higher number of aerobes. In these 3 species, if coli-group organisms occurred at all, they were in insignificant quantities. Cows had low counts with a relatively high proportion of coli-group organisms. The lactobacilli in man and guinea pig were predominantly *L. bifidus*; in the rabbit, hen and rat they were partly *L. bifidus*. In no case were coli-group organisms quantitatively the main flora of the feces. (From author's summary)

247. HARRISON, B. M. *The Dissection of the Cat (and Comparisons with Man). A Laboratory Manual on* Felis domestica. 3rd ed. St. Louis, Mosby, 1956, 217 pp.

The skeleton; muscles of the cat; general internal organs; venous and lymphatic systems; arterial system and heart; the pharyngeal region; the brain; spinal cord and peripheral nerves.

248. HINES, H. M., IMIG, C. J., AND ROBERSON, W. J. Comparison of blood flow in normally innervated and in sympathectomized legs of dogs after exposure to cold. *U.S. Air Force School of Aviation Medicine Report* 56–53: 1–7 (May), 1956.

Volume blood flow was measured by a technique of venous occlusion plethysmography in hind legs of dogs with intact innervation and in sympathectomized legs during and following rewarming after an exposure to cold and following i.v. administration of pentobarbital sodium or hexamethonium. The results are tabulated.

249. HUGHES, R., MAY, A. J. AND WIDDICOMBE, J. G. The output of lymphocytes from the lymphatic system of the rabbit. *J. Physiol. (London)* 132: 384–90 (May), 1956.

Lymph from the right lymphatic duct of anesthetized rabbits was diverted to the thoracic duct from which it was cannulated. The combined lymphocyte output from both these ducts was 29.5 $\times$ 10^8 cells/kg/day. The mean lymphocyte output from the cannulated right subclavian duct was 3.06 $\times$ 10^8 cells/kg/day; the lymph from this duct contained 3.5 gm protein/100 ml. Authors conclude that the rabbit lymphocyte lives only for about 2 hr. in the blood stream. (From author's summary)

250. IMIG, C. J., ROBERSON, W. J., GAULT, M. AND HINES, H. M. Blood flow in the hind limbs of dogs after exposure to cold. *U.S. Air Force, School of Aviation Medicine Rept.* 55–66 (Mar.), 1956.

Blood flow volume was measured in the hind limbs of dogs during and following rewarming of the tissues after exposure of parts of the extremity to various intensities and durations of cold. Blood flow was measured either by an electromagnetic flowmeter or by venous occlusion plethysmography. (Condensed from author's summary)

251. JACOBS, J. AND BROWN, J. H. U. Kidney function in the adult rat. *Am. J. Physiol.* 186: 172–4 (July), 1956.

Endogenous creatinine clearance of the adult Sprague-Dawley rat has been determined to be 0.556 ml/min/100 gm body weight. This value must be increased about 25% in order to obtain "true" creatinine clearances. Large doses of atropine or hexamethonium decreased the creatinine, Na and K clearances. The clearance of Na was decreased to a greater extent than was the creatinine or K clearance. The urinary Na/K ratio was also decreased in the presence of both drugs. (Author's summary)

252. JOHNSON, H. H., JR. Variations in histamine levels in guinea pig skin related to skin region; age (or weight); and time after death of the animal. *J. Invest. Dermatol.* 27: 159–63 (Sept.), 1956.

No significant changes in "labile" skin histamine levels in guinea pigs occurred during a 24-hr. period post mortem in animals kept at 4°C. Young guinea pigs (less than 2.5 mo. old) had skin histamine levels about twice as high as adult guinea pigs. A fairly regular relationship to body weight occurred, so that whether age or weight was the significant factor could not definitely be concluded from this experiment. (From author's summary)

253. KELLER, D. L AND UMBREIT, W. W. "Permanent" alteration of behavior in mice by chemical and psychological means. *Science* 124: 723–4 (Oct. 19), 1956.

A head-twitch response was produced in several strains of mice tested by solitary confinement. By placing the mice in separate cages (1 mouse to a cage) where they had access to light and sound but were unable to see any other mice, 30%–80% (depending on the strain employed) developed the head-shake response in 2 days. If, after 3 weeks' confinement they were returned to groups of 8–10 mice/group, about 80% retained the response for weeks or months. Treatment with reserpine relieved the head-shake temporarily but did not cure it.

254. MAKEPEACE, L. I. *Rabbits, A Subject Bibliography.* Denver, Bibliographical Center for Research, Rocky Mountain Region, 1956, 81 pp.

A bibliography consisting of 3,485 references, on all phases concerning the rabbit. An author and a subject index are included.

255. MARSHALL, L. H. AND HANNA, C. H. Direct measurement of arterial blood pressure in the guinea pig. *Proc. Soc. Exptl. Biol. Med.* 92: 31–2 (May), 1956.

In 8 guinea pigs under local or general anesthesia systolic and diastolic end pressures in the carotid artery averaged 77 and 47 mm Hg, respectively; the mean pressure was calculated to be 57 mm Hg. The technique of measurement is described.

256. NATIONAL RESEARCH COUNCIL, COMMITTEE ON THE HANDBOOK OF BIOLOGICAL DATA. *Handbook of Biological Data*, edited by W. S. SPECTOR. Philadelphia, Saunders, 1956, 584 pp.

The book contains data on biochemical and biophysical characteristics; genetics, cytogenetics and reproduction; development and morphology; nutrition, digestion and metabolism; respiration and circulation; other physiological activities and performances; biologically active compounds; environment and survival; symbiosis and parasitism; ecology and biogeography. Most laboratory animals, such as mouse, rat, rabbit, guinea pig, dog, cat, hamster, etc., are included.

257. ROMER, A. S. *Osteology of the Reptiles.* Chicago, Univ. of Chicago Press, 1956, 850 pp.

Summary, on a comparative basis, of the present knowledge of the reptile skeleton, living and fossil, and an osteologically based classification of the reptile family. The elements of the reptile skeleton are thoroughly described, tracing each through the several reptile orders. In the second part of the book, a classification of reptiles is set forth, with definitions down to the family, based on skeletal characteristics.

258. RUEGAMER, W. R. AND SILVERMAN, F. R. Influence of gentling on physiology of the rat. *Proc. Soc. Exptl. Biol. Med.* 92: 170–4 (May), 1956.

Physiological differences in weight gain, food utilization, carcass length and thyroid uptake between gentled and nongentled, single and double caged Sprague-Dawley weanling male rats were determined *1*) under normal conditions, *2*) after food restriction or electrical shock for 3 wk., *3*) under stress of starvation or shock.

259. SMITH, E. Pregnancy in the little brown bat. *Am. J. Physiol.* 185: 61–4 (Apr.), 1956.

Body weights of bats of the species *Myotis lucifugus lucifugis* increase exponentially during pregnancy. The rate of increase differs with the year. At birth the single offspring weighs 28.8% of the mother's weight. The metabolic rate increases fivefold during pregnancy but is always less than the expected metabolic rate for a nonpregnant mammal of the same weight. The heat increment of gestation is 2.2 Cal., an amount less than would be expected from the birth weight. The bat fetus is produced at a very low metabolic cost to the animal. (Author's summary)

260. SMYTHE, R. H. *Veterinary Ophthalmology.* London, Bailliere, 1956, 356 pp.

Part I of the book is concerned with the anatomy and physiology of the eye and part II with clinical ophthalmology. In the appendix, ophthalmic preparations listed in the *British Veterinary Codex* are given. Species included in the survey are primates, rabbits, dogs, cats, horses, mice, bats, fish, birds.

261. SOLIMAN, F. A. AND GHANEM, Y. S. Levels of thyrotropic and gonadotropic hormones in the blood of of mature and immature female rabbits. *Nature* 178: 745 (Oct. 6), 1956.

According to the method used (effect of s.c. injection of rabbit plasma on the weight of thyroid and testes of chicks), the thyrotropic hormone in the blood of rabbits is higher during estrus than during the stages of immaturity or pseudopregnancy. The gonadotropic hormone levels of the mature rabbits (estrous and pseudopregnant) were higher than in the immature animal.

262. STEVENS, C. E., D'ANGELO, S. A., PASCHKIS, K. E., CANTAROW, A. AND SUNDERMAN, F. W. The response of the pituitary-thyroid system of the guinea pig to low environmental temperature. *U.S. Air Force School of Aviation Medicine Rept.* 55–21 (Apr.), 1956.

The pituitary-thyroid system in the adult female guinea pig was studied during a 1- to 11-wk. period of exposure to lowered environmental temperature (7°±2°C). Analysis of the experimental data indicates that heat production in the cold-exposed

XUM

guinea pig is maintained primarily by an activation of the pituitary-thyroid system in which secretion of thyrotrophic hormone and thyroid hormone is augmented. (Condensed from author's summary)

263. THOMPSON, H. V. AND WORDEN, A. N. *The rabbit.* London, Collins, 1956, 240 pp.

As reviewed in *Veterinary Bulletin*, 27: Abstr. No. 975, 1957, this is a comprehensive review of the present knowledge of the wild rabbit. The authors have recently been engaged in research on the rabbit problem, and their experience has contributed much information, particularly to the chapters on reproduction, behavior, and control. Other chapters deal with physiology, ecology, diseases and parasites, myxomatosis, and damage to crops. There is an appendix on legislation regarding rabbits.

264. THOMPSON, W. R., MELZACK, R. AND SCOTT, T. H. "Whirling behavior" in dogs as related to early experience. *Science* 123: 393 (May 25), 1956.

Eight out of 11 dogs (Scottish terriers of a common ancestry) which from 1–8 or 10 mo. of age had been severely restricted by being reared in isolation cages so that each dog could never see any more than the floor of the cage above or the ceiling of the room, developed whirling fits (rapid jerky running in a circle, shrill yelping, barking and tail snapping and biting). The fits were set off by some change in the stimulus-environment.

265. WELLERS, G. Un dispositif simple en vue de l'étude du bilan d'azote chez le rat. (A simple arrangement for the study of the nitrogen balance in the rat.) *J. Physiol. (Paris)* 48: 755–6 (May-June), 1956.

A metabolism cage is described which permits the determination of the N balance in the rat. Data are given for an adult rat, weight 372 gm, on the following diets: *1*) semisynthetic containing 12 gm casein/100 gm ration for 22 days, *2*) ration without proteins for 14 days and *3*) diet *1* for 21 days.

266. WHITEHOUSE, R. H. AND GROVE, A. J. *The Dissection of the Rabbit, With an Appendix on the Rat.* 5th ed. London, Univ. Tutorial Press, 1956, 184 pp.

Skeleton (including a comparison of the skull of the dog and the rabbit), external features, abdominal and thoracic cavity, the neck, heart and nervous system of the rabbit are discussed. In an appendix the salient differences as applied to the rat are given.

267. WITSCHI, E. *Development of Vertebrates.* Philadelphia, Saunders, 1956, 588 pp.

The book contains sections on multiplication and maturation of germ cells, on the start of ontogenesis, and on amphibians, fishes, birds and mammals. The section on mammals, which includes laboratory animals, contains among others the following tables: selected data about newborn mammals and their development (p. 402); composition of milk in some mammals representing various ecologic types (p. 421); timetable of events related to reproduction in three murid rodents (rat, mouse, hamster) (p. 437); fetal fluid, placental type and endometrial differentiation of some eutherian mammals (horse, pig, cattle, sheep, goat, dog, cat, rabbit, rat, guinea pig) (p. 377).

268. ALEXANDER, C. S. A new simple method for indirect determination of blood pressure in the rat. *Proc. Soc. Exptl. Biol. Med.* 94: 368–72 (Feb.), 1957.

Systolic blood pressure was measured in rats by observation with the naked eye of pulsatile vibrations in the rats' tails. The accuracy of the method both in the normal and hypertensive range was proved by comparing the data with those obtained by audiometric methods and those resulting from observation of blood flow after amputating the tip of the tail. Normotensive rats, weighing 200–475 gm each, showed a systolic pressure ranging from 92–143 mm Hg, hypertensive rats, weighing 335–444 gm, 130–187 mm Hg. Measurements taken with a 7-mm cuff exceeded those obtained with a 20-mm cuff. Almost identical measurements were obtained whether the whole body or only the tail was warmed.

269. AMIN, A., CHAI, C. K. AND REINEKE, E. P. Differences in thyroid activity of several strains of mice and F_1 hybrids. *Am. J. Physiol.* 191: 34–6 (Oct.), 1957.

Thyroid secretion rate was determined in four strains of inbred mice (A/Jax, BALB/c, C_{57}BR/cd, C_{57}BL/6) and two groups of F_1 hybrids. In all genotypes thyroid secretion was consistently, but not significantly greater in males than in females.

270. ANGELOFF, S., GALABOFF, S. AND NIKOLOFF, P. Elektrophoretische Untersuchungen des infektiösen Prozesses bei Kaninchen mit experimenteller Trypanosomiasis. (Electrophoretic study of the course of experimental trypanosomiasis in rabbits.) *Z. Immunitätsforch.* 114: 464–71 (Dec.), 1957.

Electrophoretic tests of the blood sera of normal rabbits gave the following results (per cm^2): albumin 6.08, α-globulin 2.55, β-globulin 2.87, γ-globulin 2.30.

271. ANTHONY, A. AND PARSONS, J. Variation in normal sodium, potassium and calcium levels in Wistar albino rats. *Science* 125: 881–3 (May 3), 1957.

Data on day-to-day and diurnal variation of serum Na, K and Ca levels in normal CF- and SF-Wistar rats were determined by flame spectrophotometry.

272. ANTLIFF, H. R. AND YOUNG, W. C. Internal secretory capacity of the abdominal testis in the guinea pig. *Endocrinol.* 61: 121–7 (Aug.), 1957.

The effect of cryptorchidism from the time of birth until 3 yr. of age on the development and maintenance of male sexual behavior, and on the capacity of the testes to secrete hormone in amounts sufficient to maintain the genital tissues, has been investigated. (Condensed from author's summary)

273. AUSTIN, C. R. Fate of spermatozoa in the uterus of the mouse and rat. *J. Endocrinol.* 14: 335–42 (Jan.), 1957.

The uterine fluid of mice and rats sacrificed at 2–6, 14–18, and 20 hr. after coitus was examined for the number of spermatozoa and leukocytes present at the times indicated. In mice, the uterine contents are apparently evacuated about 20 hr. after coitus in spite of the continued presence of a copulation plug. Phagocytosis of spermatozoa in rats was much less extensive, probably because evacuation takes place sooner after ovulation, though still about 20 hr. after coitus.

274. AUSTIN, C. R. AND BISHOP, M. W. H. Fertilization in mammals. *Biol. Revs. Cambridge Phil. Soc.* 32: 296–349 (Aug.), 1957.

This review contains the following chapters: The gametes; spermatozoan penetrations and early reactions of the egg; activation and pronucleus formation; pronuclear development and syngamy; cytoplasmic elements in fertilization; alternatives to normal fertilization; experimental manipulation of spermatozoa and eggs. An extensive bibliography is included.

275. Baer, J. E., Peck, H. M. and McKinney, S. E. Some normal laboratory values in the dog. *Proc. Soc. Exptl. Biol. Med.* 95: 80–4 (May), 1957.

Blood and urine components were determined statistically in a large number of normal female mongrel dogs on a standard diet. The results are shown in graphs or tables. The following constituents were determined: urinary total and urea N, creatinine, bile, albumin, volume of urine and pH; plasma glucose, bilirubin, cholesterol, creatinine, total protein, urea and nonprotein N, alkaline phosphatase, potassium, sodium. Hematologic tests included erythrocytes, hemoglobin, hematocrit, reticulocytes, sedimentation rate, total leukocytes, neutrophils, lymphocytes, eosinophils, monocytes, basophils. Liver function was also measured by Bromsulphalein test.

276. Bailey, C. B., Kitts, W. D. and Wood, A. J. A simple respirometer for small animals. *Can. J. Animal Sci.* 37: 68–72 (June), 1957.

An apparatus for the indirect determination of basal metabolic rate has been described. Representative results using the Swiss albino mouse as an experimental subject are recorded. (Author's abstract)

277. Barrows, C. H., Jr., Yiengst, M. J., Shock, N. W. and Chow, B. F. Age differences in cellular metabolism of various tissues of rats. *Federation Proc.* 16: Abstr. No. 30 (Mar.), 1957.

A study of the cellular metabolism of kidney, heart and liver showed that the liver exhibits agewise changes to a lesser extent than kidney and heart.

278. Beecher, H. K. The measurement of pain. Prototype for the quantitative study of subjective responses. *Pharmacol. Rev.* 9: 59–209 (Mar.), 1957.

A review based on 687 references, covering a period of 106 years of experimental work, is presented. Reference is made to man as well as animals.

279. Benacerraf, B., Biozzi, G., Halpern, B. N., Stiffel, C. and Mouton, D. Phagocytosis of heat-denatured human serum albumin labelled with I^{131} and its use as a means of investigating liver blood flow. *Brit. J. Exptl. Pathol.* 38: 35–48, 1957.

The blood clearance of heat-denatured serum albumin labelled with I^{131} was measured in mice, rats, guinea pigs and rabbits. At high dose levels the phagocytic activity of the reticulo-endothelial system could be measured, and at low dosage levels the blood clearance could be used to estimate liver blood flow. (*Vet. Bull.* 27: 2192 (July), 1957)

280. Bloom, F. Some blood chemical constituents of normal cats. *North Am. Veterinarian* 38: 114–7, 1957.

Some blood chemical constituents, including nonprotein nitrogen, urea nitrogen, creatinine, uric acid, glucose, serum cholesterol, serum calcium, serum inorganic phosphates, serum chlorides, serum total protein, serum albumin, serum globulin, alkaline phosphatase, and acid phosphatase were studied in 10 normal cats. Significant variations from the values present in normal dogs were observed in the cats of the nonprotein nitrogen, urea nitrogen, uric acid, serum calcium, serum inorganic phosphates, serum chlorides, serum cholesterol, serum total protein, serum albumin, and serum globulin. (From author's summary)

281. Braden, A. W. H. The relationship between the diurnal light cycle and the time of ovulation in mice. *J. Exptl. Biol.* 34: 177–88 (June), 1957.

The period required for the completion of ovulation in groups of mated females has been studied in 615 mice from three random-bred stocks (L, C and PCT) and in 137 mice of mixed origin all of which had been kept for some time under 1 of 4 different diurnal light cycles. The variation between mice in any one group was greatest when they were maintained under cycles with a relatively long dark phase.

282. Burke, J. D. Blood oxygen capacity of albino rats. *Am. J. Physiol.* 188: 118–20 (Jan.), 1957.

The oxygen capacity of the blood of 64 albino *Rattus norvegicus* (Sherman strain) was determined by the microgasometric syringe method. Data were obtained showing the relationship of blood oxygen capacity to weight and sex of the animals. (Condensed from author's abstract)

283. Chai, C. K. Developmental homeostasis of body growth in mice. *Am. Naturalist* 91: 49–55 (Jan.-Feb.), 1957.

Observations of variability of body size at different periods of postnatal growth of mice from different inbred and crossbred populations have been presented. The variability following body growth was shown to decrease in both inbred and F_1 hybrid groups of mice but to increase in the backcross and F_2 generations. Inferences concerning developmental homeostasis and time of gene action have been made. (Author's summary)

284. Christianson, M. and Jones, I. C. The interrelationships of the adrenal glands of mother and foetus in the rat. *J. Endocrinol.* 15: 17–42 (Apr.), 1957.

Normal nonpregnant, pregnant and pseudopregnant albino rats were studied. Adult and fetal body and adrenal weights and fetal pituitary weights were recorded and the adrenals examined histologically. Na and K content of adult and fetal plasma and muscle and water content of muscle were determined.

285. Clarkson, T. B., King, J. S., Jr. and Warnock, N. H. Serum and tissue cholesterol levels of cholesterol-fat-fed gerbils. *Proc. Animal Care Panel* 7: 220–1 (Sept.), 1957.

In the search of a new species for the study of experimental atherosclerosis, male Mongolian gerbils, 20–30 gm weight, were fed Purina laboratory chow plus 1% (by weight) crystalline cholesterol and/or 4% peanut oil, for 10–18 wk. Necropsy revealed no signs of atherosclerotic changes. However, determination of cholesterol in serum, liver and adrenal showed that relatively low levels of cholesterol and fat sufficed to cause considerable increase in the serum and hepatic cholesterol.

286. Coles, B. L. Serum protein pattern in normal kittens. *J. Physiol. (London)* 136: 37P (Feb.), 1957.

The serum protein pattern was determined by paper electrophoresis. For the 1st 2 days of life the protein pattern reflected that of the mother; after this there was a steady fall in γ-globulin to a minimum level at 21 days, and a progressive rise after 5–6 wk. of age. The average percentage of albumin was fairly unchanged from 3 days to 24 wk. when it began to fall. α- and β-globulin showed little variation with age; total serum protein reached a minimum at 4 days and then progressed with age.

287. Davis, D. E. and Christian, J. J. Relation of adrenal weight to social rank of mice. *Proc. Soc. Exptl. Biol. Med.* 94: 728–31 (Apr.), 1957.

XUM

A pilot experiment indicated that daily handling did not influence the weight of the adrenal glands of mature "wildstrain" house mice. However, a significant relationship was found between adrenal weight and social rank (as determined by observation of fighting). High-ranking mice showed smaller adrenals than low-ranking ones.

288. DEWAR, A. D. The endocrine control of the extra-uterine weight gain of pregnant mice. *J. Endocrinol.* 15: 216–29 (June), 1957.

The effect of progesterone tablet implants upon the body weight of nonpregnant, pregnant and spayed mice was studied. It was found that the weight increase of the mouse during pregnancy is under the control of ovarian progesterone and that estrogens neither play any part in the weight gain of pregnancy nor do they exhibit luteotrophic activity.

289. DEWAR, A. D. Body weight changes in the mouse during the oestrous cycle and pseudopregnancy. *J. Endocrinol.* 15: 280–3 (June), 1957.

Apart from a tendency to a slight increase in weight at estrus, no marked cyclic alterations in body weight are evident in the mouse during the estrous cycle. In pseudopregnancy, however, a definite weight increase (av. 7%) occurs; this weight gain is rapidly lost after removal of the ovaries but may be maintained after spaying by the administration of progesterone, thus indicating a close similarity to the weight change of pregnancy. (Author's summary)

290. FAND, I. AND GORDON, A. S. A quantitative study of the bone marrow in the guinea pig through life. *J. Morphol.* 100: 473–500 (May), 1957.

The absolute numbers of hemopoietic elements and the relative concentrations of composite cellular lines in femoral bone marrow were determined in 104 guinea pigs in the neonatal, immature-mature, mature and post-mature-senile stage. Histological analysis of the bone marrow revealed a progressive fatty infiltration commencing in early maturity and reaching a peak in late senescence. In neonatal peripheral blood, erythrocyte counts, hemoglobin and hematocrit values were significantly greater than those in the adult. Within several days, however, adult values were reached and maintained throughout senescence. Leukocytes rose progressively from relatively low post-partum levels to 3–4 times these values in the senile animal.

291. FANTL, P. AND MARR, A. G. Prothromboplastin activities of some mammalian plasmas and sera. *Australian J. Biol. Sci.* 10: 351–9 (Aug.), 1957.

The rate of formation of thromboplastin was determined in several mammalian plasmas and sera. A marked difference in stability of blood thromboplastin was observed. Catechol had a stabilizing effect on blood thromboplastin. α- and β-prothromboplastin (antihemophilic factor and PTC or Christmas factor) showed no species specificity when combined with heterologous clotting components. The plasma of man, rabbit, guinea pig, and rat showed a similar range of α- and β-prothromboplastin activities. Dog plasma showed a higher activity. In addition to α- and β-prothromboplastin, other factors are required for efficient thromboplastin formation; one or more of these are present in serum and these show species specificity. (Author's summary)

292. FOLK, G. E., JR., DODGE, C. H. AND FOLK, M. A. Resting body temperatures of raccoons and domestic rabbits. *Proc. Animal Care Panel* 7: 253–8 (Dec.), 1957.

The body temperature of two wild-caught adult raccoons ranged from 99.4°F to 101.8°F (mean 100.7°F or 38.2°C). The resting temperature was 100.5°F. There was no apparent effect upon body temperature of exposure to cold for 3 days. The night temperature of each raccoon was usually 1° lower than the highest day temperature. Three control rabbits showed a mean body temperature about 2.5°F higher than the raccoons. All rabbits showed a cycle of temperature which was the reverse of the raccoons, since it dropped in the daytime and rose at night. The application of these results to defining the term semihibernation is discussed. (Author's summary)

293. FOWLER, R. E. AND EDWARDS, R. G. Induction of superovulation and pregnancy in mature mice by gonadotropins. *J. Endocrinol.* 15: 374–84 (Sept.), 1957.

The injection of one immunizing unit pregnant mares' serum (PMS) followed after 40 hr. by two immunizing units human chorionic gonadotropin (HCG), or of 3 immunizing units PMS followed by 3 immunizing units HCG into mature female mice selected at random with regard to their estrous cycle induces estrus and mating in approximately 75%, and ovulation in 99%. The induction of superovulation depends on the amount of PMS injected and on the strain of mice used. The value of the method as a technique for inducing estrus, ovulation, and pregnancy in mature female mice is considered. (Condensed from author's summary)

294. GARCIA, J. F. Changes in blood, plasma and red cell volume in the male rat, as a function of age. *Am. J. Physiol.* 190: 19–24 (July), 1957.

Using the Fe^{59}-labeled cell dilution technique, the blood, plasma and red cell volume and total circulating hemoglobin have been determined on 259 male rats varying in age from 1 to 340 days. An anemic period exists in the male rat which is maximal between 15 and 20 days of age. This anemia is observed in terms of a decrease in the volume of red blood cells/gm of rat as well as in hematocrit and hemoglobin concentration values. However, throughout this anemic period there is a continual increase in total red cell volume and, in fact, the daily gain of red blood cells/gm of rat is greater during this period than at any time thereafter. In spite of the very high rate of erythropoiesis occurring at this time the growth of the body mass as a whole exceeds it and so for a time anemia results. (Author's summary)

295. GATES, A. H. AND RUNNER, M. N. Influence of prepuberal age on number of ova that can be superovulated in the mouse. *Anat. Record* 128: 554 (July), 1957.

Superovulation was accomplished by administration of pregnant mares' serum followed 40 hr. later by an ovulatory dose of human chorionic gonadotropin. In mice induced to superovulate between 2–4 wk. of age the numbers of ova shed were found to fluctuate with the prepuberal patterns of ovagenesis and follicular atresia.

296. GOY, R. W., HOAR, R. M. AND YOUNG, W. C. Length of gestation in the guinea pig with data on the frequency and time of abortion and stillbirth. *Anat. Record* 128: 747–57 (Aug.), 1957.

An analysis of pregnancies was made in 1,116 genetically heterogeneous and in 295 strain 13 guinea pigs. The mean length of gestation for litters containing living young varied inversely with size: In the genetically heterogeneous females, it was 71 days for litters of 1 and 67 days for litters of 5 and 6. Abortions in these groups occurred any time prior to 67 and 62 days, respectively. Only stillborn were delivered when the gestation period exceeded 74 days for litters of 1–3 and 71 days for litters of 6. In strain 13 females, incidence of abortions and stillbirths was higher. (From author's summary)

297. HALBERG, F., HAMERSTON, O. AND BITTNER, J. J. Sex difference in eosinophil counts in tail blood of mature B_1 mice. *Science* 125: 73 (Jan. 11), 1957.

Eosinophil counts, made in tail blood of a subline of C57 black stock (B_1) mice, showed lower levels in females than in males. The mean paired adrenal weights and the ascorbic acid concentration in the adrenals were higher in females than in males.

298. HELLMANN, K. AND COLLINS, K. J. Thyroid, salivary and Harderian glands in mice exposed to heat. *J. Endocrinol.* 15: 145–50, 1957.

Uptake of I^{131} by the thyroid, submaxillary and Harderian glands was measured in CBA, C57, RIII and A inbred strains and F_1 hybrid mice, reared in a hot environment (91° ± 1°F dry bulb, 85° ± 1°F wet bulb) or in an ordinary environment (68° ± 3°F, D.B., 65° ± 3°F, W.B.).

299. HERMAN, J. A. Electrophorèse sur papier du serum de chien normal. (Electrophoresis on paper of normal dog serum.) *Rev. belge pathol. et méd. exptl.* 26: 106–11 (Apr.), 1957.

The serum proteins were determined for normal dogs by paper electrophoresis. The results obtained were compared with those of other authors and those obtained previously by the Tiselius method of cellular electrophoresis.

300. HEROUX, O. AND ST. PIERRE, J. Effect of cold acclimation on vascularization of ears, heart, liver and muscles of white rats. *Am. J. Physiol.* 188: 163–8 (Jan.), 1957.

The degree of vascularization of different tissues of rats killed with ether after a 4-wk. acclimation period to 30°C or 6°C was estimated by counting on benzidine stained cross sections, capillaries in heart and leg muscles (soleus, gastrocnemius, plantaris), sinusoids in liver and all blood vessels in ears. The techniques of counting capillaries and fibers are discussed. (Condensed from author's summary)

301. HOAR, R. M., GOY, R. W. AND YOUNG, W. C. Loci of action of thyroid hormone on reproduction in the female guinea pig. *Endocrinology* 60: 337–46 (Mar.), 1957.

Observation that the percentage of premature births is higher in strain 13 guinea pigs (inbred, hypothyroid strain) than in any other strains or stocks, led to the investigation of the loci of action of the thyroid hormone on reproduction. The percentage of sterile matings and of resorptions and absorptions, the days of gestation when resorption or abortion occurred, the per cent stillborn, average litter size and average gestation in days are tabulated for thyroxin-treated and control guinea pigs of this strain and genetically heterogeneous animals.

302. HOAR, R. M. AND YOUNG, W. C. Respiratory metabolism during pregnancy in the guinea pig. *Am. J. Physiol.* 190: 425–8 (Sept.), 1957.

Oxygen consumption and heart rate during pregnancy were measured in normal, thyroxin-injected and thyroidectomized guinea pigs, given I^{131}. The measurement equipment used is described.

303. HORGER, L. M. AND ZARROW, M. X. Certain endocrine aspects of the anemia of pregnancy in the rabbit. *Am. J. Physiol.* 189: 407–11 (June), 1957.

The anemia of late pregnancy in the rabbit was found to be normochromic and normocytic and appeared to be due to a hemodilution since both the blood and plasma volume were increased. No significant change in the thiocyanate space was observed. A similar anemia was induced by treatment with 1 mg of estradiol daily except that an increase in the thiocyanate space was also noted. Progesterone alone had no effect, but modified the action of estradiol on blood and plasma volumes when administered in combination. It was concluded that although estrogen and progesterone may play important roles in the fluid metabolism of the pregnant female, they are not the sole etiologic agents in the anemia of pregnancy in the rabbit. (Condensed from author's summary)

304. HRUBANT, H. E. A chromatographic analysis of the free amino acids in the blood plasma of three inbred strains of the house mouse, *Mus musculus*. Thesis, Ohio State University, 1957, 145 pp.

Mice of the following three strains were studied: SEC/2 Gn-d, CBA/Ca-se and the Furless strain, statistically significant differences were found between the genotypes in the SEC/2 Gn-d strain for glutathione, glycine, α-alanine and valine-norvaline. No differences were found among the genotypes in the CBA/Ca-se strain. Significant differences were found in the Furless strain with respect to glutathione, aspartic acid, lysine and iso-leucine-leucine. Significant differences were found in the level of arginine, lysine, valine-norvaline and glutamic acid between the sexes of each particular strain. (*Dissertation Abstr.* 18: 1158–9, 1958)

305. HUDSON, G. Bone marrow volume in guinea pigs. *Nature* 179: 1032–3 (May 18), 1957.

A method for measuring the volume of bone marrow in male guinea pigs of the Dunklin-Hartley strain is described. The mean marrow volume of 25 guinea pigs, 350–450 gm, was 7.014 ml, SD 0.358. In guinea pigs, weighing 85–1250 gm, a linear relationship was found between marrow volume and the logarithm of body weight. About 50% of the marrow was in the limb bones, 20% in the skull and the rest in the trunk. Fatty marrow was found to be confined to the periphery of the limbs and coccyx, red marrow occupied all the other bones. In 12 animals, 350–450 gm weight, the mean red marrow volume was 6.249 ml, representing 89% of the total marrow.

306. JOHNSON, H. D., CHENG, C. S. AND BRODY, S. Effect of rising environmental temperature on the thyroid I^{131} activity. *Federation Proc.* 16: Abstr. No. 295 (Mar.), 1957.

Rising environmental temperature (48°–110°F) caused a decrease of thyroid activity in both male and female rabbits. Associated with declines of thyroid activity were decreases in food consumption and heat production and a rise of rectal temperature.

307. JOHNSON, H. D., RAGSDALE, A. C. AND CHENG, C. S. Environmental physiology and shelter engineering with special reference to domestic animals. XLV. Comparison of the effects of environmental temperatures on rabbits and cattle. Part 1—Influence of constant environmental temperatures (50° and 80°F.) on the growth responses and physiological reactions of rabbits and cattle. *Missouri Univ. Agr. Expt. Sta. Research Bull.* No. 646 (Nov.), 1957, 52 pp.

Metabolic factors in rabbits such as growth and development were found to be primarily dependent upon the ease with which the animals could dissipate their heat. Constantly high temperatures (80°–83°F) had a depressive effect on growth and development. Thyroid activity was higher in cold-reared animals,

which also grew faster, and increased with age. Hypotheses concerning the mechanism of the effect of high temperatures are advanced.

308. JOHNSON, T. N. Studies on the brain of the guinea pig. I. The nuclear pattern of certain basal telencephalic centers. *J. Comp. Neurol.* 107: 353–77 (June), 1957.

The nuclear configuration and cytoarchitecture of the olfactory bulb, accessory olfactory formation, anterior olfactory nucleus, septal area, tuberculum olfactorium, and amygdala in the guinea pig are described and illustrated.

309. LATEGOLA, M. T., MASSION, W. H. AND SCHILLING, J. A. Physiologic and morphologic effects of lung resection in dogs. Mechanics of breathing, gas exchange, pulmonary arterial pressure, compliance, and lung weights. *U.S. Air Force, School of Aviation Medicine Rept.* 57–65 (Apr.), 1957, 8 pp.

Oxygen consumption and pulmonary artery pressure were recorded in mongrel dogs before and after resection of 41.1% of the animal's lung.

310. LATIMER, H. B. AND SAWIN, P. B. Morphogenetic studies of the rabbit. XV. Measurements of the digestive tube and of its parts in normal and dwarf rabbits of race X. *Anat. Record* 129: 1–16 (Sept.), 1957.

Tables are given for weights and percentage weights of the digestive tube and its parts in normal and dwarf male and female rabbits; also lengths, multiples of body length and percentages of the digestive tube length in normal and dwarf rabbits.

311. LEVI, W. M. *The Pigeon.* Sumter, S. C., Levi Publishing Co., 1957, 667 pp.

The book contains the following chapters: The relationship of pigeon and man; breeds and varieties; anatomy; physiology; genetics—variation and inheritance; practical breeding; behavior; diseases, parasites, and pests—their treatment and control; feeds and feeding; housing; commercial squab production; the pigeon fancy—exhibiting, racing, etc. An extensive bibliography is included.

312. MACFARLANE, W. V. Endocrine adaptations to the tropics. Paper presented at 32d meeting of Australian and New Zealand Assoc. Advancement Sci. *J. Am. Med. Assoc.* 164: 319 (May 18), 1957.

By periods of living in temperatures above 30°C, metabolic rate and thyroid activity were depressed in rats, sheep and man, food intake was reduced and water intake increased. The metabolically active components of adrenal steroid secretion also appeared depressed during hot seasons and elevated during the cooler ones. In rats and rabbits large numbers of fetuses resorb if the animal is maintained at temperatures of 35°C. Supplementary thyroid hormone, increased protein and vitamin intake or supplementary progesterone can save some fetuses from resorption. Acclimatization will protect the fetus even though ovulations are reduced for 1 mo. Protection by acclimatization is counteracted by injections of 2 mg cortisone/day.

313. MACHADO, A. B. M. Sex recognition in new-born mice. *Rev. brasil. biol.* 17: 521–3, 1957.

A method for sex recognition, based on differences of the vascular pattern of the genital papilla, was proposed and tested successfully in 306 mice from both albino and pigmented strains. In 198 of these mice the anogenital distance was also measured and the following values were obtained: males 1.94 ± 0.07 mm (range 1.6–2.2), females 1.09 ± 0.12 mm (range 0.7–1.5).

314. MOGENSON, G. J. AND JAQUES, L. B. The effect of psychological stress procedures on the prothrombin time of rats. *Blood* 12: 649–56 (July), 1957.

Forced jumping in the Lashley jumping apparatus, maintenance in cages with an electrified water source, transportation, sound-induced seizures, and electroconvulsive treatment were used in studying the effects of psychological stress on the prothrombin time of the albino rat. (Condensed from author's summary)

315. MONDINI, S. AND VENTUROLI, M. Il lipidogramma normale di cane. (Normal lipidogram of dogs.) *Atti soc. ital. sci. vet.* 11: 341–4, 1957.

Three lipid fractions, α-, β- and γ-lipoprotein, were separated in the normal blood serum of dogs by paper electrophoresis. The α-lipoproteins presented the largest fraction. 100 cc of blood serum were found to contain 243 mg cholesterol and 455 mg phospholipids (lecithin, cephalin, sphingoin).

316. PANTELOURIS, E. M. *A Handbook of Animal Physiology.* London, Bailliere, 1957, 255 pp.

A beginner's text dealing with microorganisms and higher life forms. Response and response mechanisms, nutrition and oxygen exchange, energy-yielding processes, internal environment and its regulation, and reproductive functions are covered.

317. RIEDESEL, M. L. AND FOLK, G. E. JR. Serum magnesium changes in cold-exposed mammals. *J. Mammalogy* 38: 423–4 (Aug.), 1957.

Serum Mg levels increased in hibernating bats, thirteen-lined ground squirrels, golden hamsters and black bears but did not become elevated at cold exposure without hibernation.

318. ROSS, S., FISHER, A. E. AND KING, D. Sucking behavior: A review of the literature. *J. Genet. Psychol.* 91: 63–81 (Sept.), 1957.

The review of 57 references deals with the relationship of sucking behavior to later behavior. The mechanics of the sucking response, the significance of sucking experience and the problem of artificial feeding are discussed. (57 references)

319. SCOTT, J. P. Abnormal behavior in dogs and other domestic animals. Paper presented at 7th Gaines Vet. Symposium, Kankakee, Ill., Oct. 23, 1957, pp. 2–4.

The essential factors necessary to produce functional abnormal behavior (as exemplified in mice) are hyperexcitation and hypermotivation, lack of escape and of the possibility of adaptation and genetic susceptibility. General types of behavior were studied in several breeds of dogs, those likely to be involved in functional abnormal behavior being ingestive, allelomimetic, agonistic, sexual and care-giving behaviors.

320. THOMPSON, W. R. Influence of prenatal maternal anxiety on emotionality in young rats. *Science* 125: 698–9 (Apr. 12), 1957.

On the basis of results obtained, the tentative conclusion is offered that there are some grounds for supposing that prenatal maternal anxiety in rats increases the emotionality of the offspring.

321. WALKER, D. O. AND WIRTSCHAFTER, Z. T. *The Genesis of the Rat Skeleton.* Springfield, Ill., C. C. Thomas, 1957, 59 pp.

The development of the skeleton of rats of Long-Evans strain up to 53 days after conception is presented in the form of roentgenograms and photographs of alizarin-stained specimens, showing the development of *1)* the skull and neck, *2)* the extremities, *3)* the axial and appendicular skeleton. The techniques used are described briefly. A detailed chronology of the ossification centers with time of appearance in rats after conception is shown in chart form.

322. ADAMS, W. E. *The Comparative Morphology of the Carotid Body and Carotid Sinus.* Springfield, Ill., C. C. Thomas, 1958, 302 pp.

A detailed discussion is given of the comparative anatomy, histology and embryology of the carotid body and carotid sinus of numerous species of mammals, birds, reptiles, amphibians and fish, including macroscopic and microscopic anatomy, embryology and function. (From a review in *J. Am. Vet. Med. Assoc.* 134: 45 (Jan.), 1959)

323. ALLEN, R. C. AND WATSON, D. F. Paper electrophoretic analysis of rabbit serum as an aid in the selection of experimental rabbits. *Am. J. Vet. Research* 19: 1001–3 (Oct.), 1958.

Serum protein percentages were determined for 18 adult normal rabbits and 11 with various pathological conditions, by taking the average of 3–4 blood samples from each animal. Data for 14 rabbits with clinically established cases of coccidiosis caused by *Eimeria stiedae* were based on one blood sample per animal. Serum protein migration values were shown for normal rabbits. The use of paper electrophoresis as an aid in the selection of normal animals for experimental investigations was demonstrated.

324. ANDERSEN, A. C. AND GEE, W. Normal blood values in the beagle. *Vet. Med.* 53: 135–8 (Mar.), 1958.

Blood values (erythrocytes, packed cell volume, hemoglobin, sedimentation rate, leukocytes) in the dog have been presented from embryonic development to the age when senility becomes manifest. Definite trends are apparent during the 1st yr. of life. At 1 yr. of age blood values are characteristic of those found in the adult. A diurnal pattern with physiological variations (gestation, lactation) and sex differences were noted. This diurnal pattern was similar to that reported for other species.

325. ANONYMOUS. "Hemo the Magnificent" to be televised again. *J. Am. Vet. Med. Assoc.* 132: 225 (Mar. 1), 1958.

Photomicrography of the actual flow of blood in hamsters is demonstrated in a TV program "Hemo the Magnificent" in the Bell System Science Series on blood and its circulation. The film can be procured from the Bell Telephone Co.

326. AZARNOFF, D. L. Species differences in cholesterol biosynthesis by arterial tissue. *Proc. Soc. Exptl. Biol. Med.* 98: 680–3 (Aug.-Sept.), 1958.

Coronary arteries and aortas of humans and aortas of dogs, cats, and rats cannot incorporate C^{14}-labeled acetate into cholesterol *in vitro*. Aortas of guinea pigs, rabbits, and chickens can accomplish this conversion. (Author's summary)

327. BARTLETT, R. G., JR., MANTEL, N., FOSTER, G. L. AND BERNSTEIN, P. Core to surface thermal gradients in the rat at several environmental temperatures. *Am. J. Physiol.* 193: 541–6 (June), 1958.

Clipped (restrained and nonrestrained) and nonclipped (restrained and nonrestrained) adult male rats were exposed to varying cold environments. Colonic, subcutaneous and cutaneous temperatures were measured. Restraint produced hypothermia at low temperatures (0° and 8°C) and at higher temperatures (16° and 28°C) it resulted in the virtual disappearance of the normal subcutaneous to skin surface temperature gradient. It was also observed that when the severity of stress was increased (e.g. by lowering the temperature of the cold room or adding clipping to the cold stress) the thermolability among the individuals of a group of restrained animals not only increased but also appeared to be more uniform. Thus with mild stress (e.g. clipping with severe cold or restraint with mild cold) only some of the animals showed thermolability but with a more severe stress all animals became hypothermic. (Author's abstract)

328. BARTLETT, R. G., JR. AND QUIMBY, F. H. Heat balance in restraint (emotionally) induced hypothermia. *Am. J. Physiol.* 193: 557–9 (June), 1958.

Hypothermia produced by restraint in the rat was shown to be due to an increased rate of heat loss (rather than to a decreased heat production) as a result of: *a)* a greater effective body surface exposure in the restrained rat as compared to the nonrestrained control animal (effective body surface exposure is that portion of the surface radiating to objects other than opposing areas of the animal's own body surface); *b)* a greater rate of heat loss per unit of effective body surface exposure in the restrained rat as compared to the nonrestrained control. (Author's abstract)

329. BENNETT, E. L., ROSENZWEIG, M. R., KRECH, D., KARLSSON, H., DYE, N. AND OHLANDER, A. Individual, strain, and age differences in cholinesterase activity of the rat brain. *J. Neurochem.* 3: 144–52, 1958.

Cholinesterase activity in the cortical and subcortical brain and brain weight varied significantly in the two strains of rats studied. There were also significant effects of age for each of these variables. It was thus established that cholinesterase activity in the rat brain and brain weight of the rat differ according to genetic background, age and individual factors.

330. BIGGERS, J. D., ASHOUB, M. R., MCLAREN, A. AND MICHIE, D. The growth and development of mice in three climatic environments. *J. Exptl. Biol.* 35: 144–55 (Mar.), 1958.

Pregnant mice were placed in rooms at hot, temperate and cold temperatures. The hot and cold environments were less favorable than the temperate as judged by incidence of both prenatal and postnatal mortality of the young. An inverse relationship between body weight and number of mice in a litter was particularly marked in the cold. Growth and development were retarded in the cold.

331. BIRREN, J. E. AND KAY, H. Swimming speed of the albino rat: I. Age and sex differences. *J. Gerontol.* 13: 374–7 (Oct.), 1958.

An apparatus used in a study of possible age differences in the speed of a continuous task such as swimming, in Sprague-Dawley albino rats is described. Statistically significant age differences were found for both males and females; in all instances the females were the faster swimmers.

332. BLACKLEDGE, G. T. Semen production and reserves of dogs under two management and nutritional regimes. Thesis, Cornell, 1958, 49 pp.

The effect of diet and exercise on semen quality, spermatozoa production, and libido in dogs was studied. Spermatozoa production and motility was lower on a standard diet with free exercise than on a commercial diet with limited exercise. Recovery

of spermatozoa production was complete in each group after 5 days' rest. (*Cond. Vet. Bull.* 36: Abstr. No. 2980, 1959)

333. BLANDAU, R., JENSEN, L. AND RUMERY, R. Determination of the pH values of the reproductive-tract fluids of the rat during heat. *Fertility and Sterility* 9: 207–14 (May-June), 1958.

The pH values of the fluids of the cornua, the dilated ampullae, and the periovarial sacs were determined in 67 sexually mature rats in heat. The average pH for the right cornu was 7.72 (range 7.43 to 8.31, $\sigma = 0.15$); for the left it was 7.76 (range 7.63 to 8.04, $\sigma = 0.12$). The average pH for the pooled fluids from the ampullae of the oviducts was 8.04 (range 7.31 to 8.53, $\sigma = 0.25$). The pH of the pooled fluids of the periovarial sacs averaged 8.05 (range 7.66 to 8.41, $\sigma = 0.23$). The fluids from the reproductive tract were significantly more basic than the peritoneal fluids. (Author's summary)

334. BOND, C. F. Blood volume changes in the lactating rat. *Endocrinology* 63: 285–9 (Sept.), 1958.

Plasma volume (dye method), hematocrit value, and hemoglobin and plasma protein concentrations were measured in normal female rats at two stages of lactation and 2 wk. postlactation, and from these data total blood and erythrocyte volumes and total hemoglobin were calculated. There was no correlation between maternal blood picture and litter size, but there was a high inverse correlation between litter size and the body weight of the offspring at the end of lactation. It is suggested that the increase in the volume of circulating erythrocytes constitutes a lactation polycythemia, the function of which may be to increase the oxygen-carrying capacity of the blood to meet the increased metabolic demands of lactation. (Condensed from author's abstract)

335. BOST, J. AND BLANDIN, J. L'épreuve de Thorn, chez le chien normal. (A test for adrenal cortical function in dogs.) *Rev. méd. vét.* 109: 146–52, 1958.

The authors applied to dogs the test for adrenal cortical insufficiency described by Thorn *et al.* for use in man. An i.m. injection of 10 I.U. cortiocotrophin caused eosinopenia in 10 healthy starved dogs, with greatest effect 7 hr. after injection. (*Vet. Bull.* 28: Abstr. No. 2286, 1958)

336. BOTHWELL, T. H., PRIBILLA, W. F., MEBUST, W. AND FINCH, C.A. Iron metabolism in the pregnant rabbit. Iron transport across the placenta. *Am. J. Physiol.* 193: 615–22 (June), 1958.

Iron metabolism of pregnant New Zealand white rabbits and particularly the Fe transport across the placenta at varying stages of pregnancy have been studied.

337. BRADEN, A. W. H. Strain differences in the incidence of polyspermia in rats after delayed mating. *Fertility and Sterility* 9: 243–6 (May-June), 1958.

The incidence of polyspermic eggs in rats in which copulation had been prevented until after ovulation was investigated, using two highly inbred strains (WAG albino strain and PVG hooded strain). A significant difference between the two strains was found; there was also a significant difference in incidence of polyspermia between one of the strains and F_1 females produced by crossing the two strains. Variation between strains in the proportion of eggs in which more than one sperm had penetrated the zona pellucida are shown to be partly responsible, in some instances, for strain differences in the incidence of polyspermic eggs. (Condensed from author's summary)

338. BRAITHWAITE, J. L., ADAMS, D. J. AND JONES, R. O. Arterial patterns in the spleen of normal and tumour bearing animals. *Brit. J. Cancer* 12: 242–7 (June), 1958.

The arterial patterns of the spleen have been studied in 30 normal and 30 tumor bearing rats by a radiological technique. A radiopaque medium of either micropaque, thorotrast or diaginol was injected into the abdominal aorta, the splenic artery or one of its hilar branches in the living animal or in an animal recently killed by coal gas. Radiographs on Kodaline film were taken during the course of injection and at various times after this with the spleen already in position on the plate.

339. BRASSEUR, L., ISAAC-MATHY, M. AND DE MEYER, R. Étude comparative de la teneur en glycogène du foie foetal et du placenta chez la rate gravide. (Comparative study of the glycogen content of fetal liver and placenta in the pregnant rat.) *Ann. endocrinol.* (*Paris*) 19: 431–41 (Mar.-Apr.), 1958.

The glycogen content of liver, heart, maternal skeletal muscle, placenta and fetal liver was determined in 92 pregnant Wistar rats as it varies daily from the 12th to the 21st day of gestation.

340. BURGOS, M. H. AND WISLOCKI, G. B. The cyclical changes in the mucosa of the guinea pig's uterus, cervix and vagina and in the sexual skin, investigated by the electron microscope. *Endocrinology* 63: 106–21 (July), 1958.

During estrus, the uterine epithelial cells, the superficial mucous cells of the cervical epithelium and the basal and prickle cells of the vaginal epithelium display microvilli on their surfaces which disappear during diestrus. Throughout the cycle in the cervix and during diestrus in the vagina the superficial epithelial cells are filled with large droplets of a mucus-like material. During estrus in the vagina and at all times in the sexual skin the uppermost epithelial cells consist mainly of filaments which in the basal cells occur in small clusters. (From author's summary)

341. CARPENTER, K. J. AND MAYER, J. Physiologic observations on yellow obesity in the mouse. *Am. J. Physiol.* 193: 499–504 (May), 1958.

Yellow mice of the YZ strain, obtained from the Brown University colony, were mated with Swiss albino mice (Taconic Farm strain 63), and the offspring, all yellow- and black-coated, were used for the experiments. Yellow obese mice were longer than nonobese littermates and yellow males were heavier than yellow females. Weight gain was greatest on high fat diets. If the yellow mice were given access to exercise (activity cages), they lost weight. Resistance to cold was good. Fasted blood glucose levels were normal, fed levels frequently elevated in males. Yellow male and female mice showed a degree of insulin resistance; yellow males showed a marked hyperglycemic response to growth hormone, ACTH, cortisone, and glucagon. Blood total lipids were elevated in yellow mice, with the females exhibiting hypercholesterolemia. As in other forms of 'metabolic' obesity, blood ketones were decreased by an 18-hr. fast. (Author's abstract modified)

342. CARSON J. R., JUNNILA, W. A. AND BACON, B. F. Sexual maturity and productivity in the chicken as affected by the quality of illumination during the growing period. *Poultry Sci.* 37: 102–12 (Jan.), 1958.

Crossbred cockerels and pullets were illuminated with various colored lights from 15 wk. of age through maturity; in two control treatments continuous light was provided from a 60-watt incandescent lamp, or no light other than daylight was furnished. The 60-watt lamps produced no harmful effect on livability or

egg production of the pullet; any light used stimulated the onset of egg production. Sperm production in the males was also enhanced by lighting.

343. CHAI, C. K. Endocrine variation. Thyroid function in inbred and F_1 hybrid mice. *J. Heredity* 49: 143–8 (July-Aug.), 1958.

A study has been made of thyroid activity in mice of four inbred strains and two of their F_1 hybrids, BAF_1 and BDF_1.

344. CHAMBERS, R. M. AND FULLER, J. L. Conditioning of skin temperature changes in dogs. *J. Comp. and Physiol. Psychol.* 51: 223–6 (Apr.), 1958.

Some characteristics of surface and internal temperature responses of dogs exposed to selected unconditioned and conditioned stimuli are summarized. The restrained dogs received presentations of the metronome in the preconditioning and extinction phase and an additional 2 sec. high-voltage shock in the conditioning phase. Temperatures of muzzle, dorsal and ventral surfaces of the pinna, and the rectum were recorded throughout the experiment. The temperature-response curves obtained were found to be useful indicators of autonomic arousal in the intact dog.

345. CHANG, M. C. AND THORSTEINSSON, T. Effects of urine on motility and fertilizing capacity of rabbit spermatozoa. *Fertility and Sterility* 9: 231–7 (May-June), 1958.

The motility of sperm decreased, and the concentration of reducing substances increased, as the proportion of urine contamination increased. The fertilizing capacity of sperms as determined by the percentage of ova fertilized and the transportation of sperm from vagina to the fallopian tubes as determined by the number of sperms on the zona pellucida of ova, were not disturbed even when sperms were suspended in 50% urine. When normal rabbit semen was suspended in 75% urine practically no sperm was motile, and yet up to 30% of ova were fertilized. (Condensed from author's summary)

346. COHEN, C. On blood groups and confusion in the rabbit. *Transplantation Bull.* 5: 21–3 (Jan.), 1958.

A system of nomenclature for blood groups is proposed, which encompasses earlier findings in rabbit blood groups studied genetically, is compatible with the system applying to mammalian genetics and gives direct indication of both phenotype and genotype in the symbolism. A table giving a summary of all existing symbols known to the author is included.

347. CRISCUOLO, D. Blood volume in rats chronically exposed to altitude in combination with heat. *U. S. Air Force, School of Aviation Medicine Rept.* 58–36 (Jan.), 1958, 4 pp.

Blood volume was measured in normal adult male Sprague-Dawley rats at ground level and 18,000 ft. altitude, at 25° and 35°C, respectively. No change in plasma volume was noted in any group. The altitude groups (at 25° and 35°C) showed a significant increase in cell volume and total volume.

348. CROWCROFT, P. AND ROWE, F. P. The growth of confined colonies of the wild house-mouse (*Mus musculus* L.): The effect of dispersal on female fecundity. *Proc. Zool. Soc. London* 131: 357–65 (Nov.), 1958.

Post-mortem examination of female house mice from a confined population showed a higher proportion of nonfecund females than would be found in a wild-caught sample of similar age composition. A similar population was allowed to disperse into a larger pen, whereupon the reproductive rate increased. The result was not clear-cut, however, as the increase began too soon to be attributable to dispersal alone. Another similar population was divided into two colonies of unequal size. Nonfecund females transferred to a new large pen with few other mice became fecund and reproduced successfully, while those placed in a new small crowded pen remained nonfecund. A completely adult population in which no litters had been born for over 6 mo. was allowed to disperse into a large pen. A majority of females became fecund and conceived within about 1 wk. The numbers were doubled within 8 wk. The results suggest the existence of a self-regulatory mechanism, which operates at population densities seldom, if ever, reached in free-living populations. (Author's summary)

349. D'ANGELO, S. A. AND TRAUM, R. E. An experimental analysis of the hypothalamic-hypophysial-thyroid relationship in the rat. *Ann. N. Y. Acad. Sci.* 72, Art. 7: 239–70 (Oct. 10), 1958.

Thyroid secretion was assessed in adult female Wistar albino rats by an *in vivo* detection method in which the biological decay of I^{131} from the gland was measured over the neck of the rat by a γ-sensitive Geiger-Müller tube. Conclusions were drawn concerning the role of the hypothalamus in the hypothalamic-hypophysial-thyroid system.

350. DAVIS, D. H. S. AND OETTLÉ, A. G. The multimammate mouse *Rattus* (*Mastomys*) *natalensis* Smith: A laboratory-adapted African wild rodent. *Proc. Zool. Soc. London* 131: 293–9 (Sept.), 1958.

Similarities and differences between the multimammate mouse, the laboratory rat and laboratory mouse are tabulated and the taxonomic status of the multimammate is discussed. The use of this rodent in *Schistosoma* and in cancer research is pointed out.

351. DEBIAS, D. A., PASCHKIS, K. E. AND CANTAROW, A. Effects of chlorpromazine and autonomic nervous system blocking agents in combating heat stress. *Am. J. Physiol.* 193: 553–6 (June), 1958.

The number of normal rats of the Wistar strain surviving exposure to a temperature of 37.5°–38.5°C for a period of 6 hr. was significantly greater than the number of adrenalectomized rats similarly exposed. The observations suggest that the mechanisms of protection against heat and cold exposure differ from those involved in protection against other types of stress.

352. DENENBERG, V. H., SAWIN, P. B., FROMMER, G. P. AND ROSS, S. Genetic, physiological and behavioral background of reproduction in the rabbit: IV. An analysis of maternal behavior at successive parturitions. *Behaviour* 13: 131–42, 1958.

The following four aspects of maternal behavior were studied: interest in young, time of nestbuilding, preparturient and postparturient aggression. A summary of the results is tabulated.

353. DERIVAUX, J. *Physio-Pathologie de la Reproduction et Insémination Artificielle des Animaux Domestiques.* (*Physio-Pathology of the Reproduction and Artificial Insemination of Domestic Animals.*) Paris, Vigot Frères, 1958, 466 pp.

The author states that the book (with 400 references) is meant to be useful for people engaged in fundamental research and for those who are trying to make application of the fundamental precepts. The highly favorable review in the *J. Am. Vet. Med. Assoc.* 134: 482 (May), 1959, calls particular attention to the

table of contents that serves as a valuable guide in approaching a clinical problem in reproduction.

354. Diesem, C. D., Venzke, W. G. and Moore, E. N. The hemograms of healthy chickens. *Am. J. Vet. Research* 19: 719–24 (July), 1958.

Leukocyte, thrombocyte and erythrocyte counts of healthy chickens, 5–10 wk. old, were reported. A microhematocrit method of determining blood cell volume was found to be a useful diagnostic aid in the study of avian blood.

355. Dobberstein, J. and Koch, T. *Lehrbuch der vergleichenden Anatomie der Haustiere.* (*Textbook on Comparative Anatomy of Domestic Animals.*) 3rd ed. Leipzig, S. Hirzel, 1958, 234 pp.

The first chapter describes the circulatory and lymphatic systems of various species of domestic animals; the 2nd discusses the central and peripheral nervous system; the 3rd deals with sensory organs; and the last chapter is devoted to the skin, udder, hoofs, claws, nails, and horns. (Abstr. *J. Am. Vet. Med. Assoc.* 134: 379 (Apr. 15), 1959)

356. Doggart, J. R., McCredie, J. A. and Welbourn, R. B. Urinary excretion of amino-acids in normal dogs and in those with experimentally-induced cirrhosis and with altered blood supply to the liver. *Vet. Record* 70: 279–82 (Mar.), 1958.

A paper-chromatographic method has been used in the study of the amino acid excretion in the urine of dogs. The normal pattern, containing taurine, methylhistidine, and glutamine as the strongest spots, is described together with its daily variation. The effects on the amino acid excretion of portacaval anastomosis and total arterialisation of the blood supply to the liver of the normal and cirrhotic dog have been described; taurine and glutamine are most sensitive to these procedures. The excretion in estrus and pregnancy is abnormal. (Author's summary)

357. Everitt, A. V. The urinary excretion of protein, non-protein nitrogen, creatinine and uric acid in ageing male rats. *Gerontologia* 2, No. 1: 33–46, 1958.

The urinary excretion of protein in the male rat increased sharply with age, showing a tenfold increase from youth to senility. The excretion of creatinine decreased progressively with age, commencing in middle age and reaching the lowest level just before death. The excretion of both uric acid and nonprotein nitrogen, expressed as mg/gm of food consumed, increased in middle age when growth ceased. A second rise in the excretion of these constituents occurred in the last 200 days of life, as the rat approached death. The age changes in the excretion of nonprotein nitrogen, creatinine and uric acid were not affected by the presence of renal disease associated with a high protein excretion. (Author's summary)

358. Everitt, A. V. The electrocardiogram of the ageing male rat. *Gerontologia* 2, No. 4: 204–12, 1958.

Electrocardiograms were recorded in male albino rats of a non-inbred Wistar strain in young adult life at 300 days, in middle age at 540 days, in old age at 715 days and in senility at 900 days. At necropsy the moist weight of the heart ventricles was determined in 22 rats surviving until senility and in 20 young male rats sacrificed in young adult life. All data were statistically evaluated.

359. Everitt, A. V. and Webb, C. The blood picture of the aging male rat. *J. Gerontol.* 13: 254–60 (July), 1958.

In male rats of the Wistar strain, both the hemoglobin level and the red cell count in tail blood increased from old age to senility. The eosinophil count decreased progressively with age, falling most sharply in the last 50 days of life. Severe lung disease had no significant effect on these age changes in hemoglobin level, red cell count, and eosinophil count. On the other hand, the white cell count increased significantly with age in rats that developed severe lung disease, but not in those with healthy lungs at autopsy. (Author's summary)

360. Folk, G. E., Jr. and Grindeland, R. E. Estrous cycles of cold-exposed hamsters. *Anat. Record* 132: 447–8 (Nov.), 1958.

The effect of cold exposure and hibernation on the estrous cycle and the body weight of golden hamsters was studied.

361. Frankel, H. M. and Folk, G. E., Jr. Heat tolerance in rats and hamsters. *Physiologist* 1, No. 4: 23, 1958.

The survival time of male rats and male and female hamsters to environmental temperatures ranging from 40°–60° and 40°–50°C, respectively, was determined. Confinement to a small space reduced survival time. Sex, body weight, body surface or initial body temperature did not affect survival time. Animals exposed to temperatures of 45°C and above at autopsy showed vascular engorgement and pulmonary edema.

362. Frankel, H. M., Folk, G. E., Jr. and Craig, F. N. Effects of type of restraint upon heat tolerance in monkeys. *Proc. Soc. Exptl. Biol. Med.* 97: 339–41 (Feb.), 1958.

Macaca monkeys attached to an animal board by means of the wrists and ankles with arms and legs extended, in an environment of 38°C and 45% relative humidity, were unable to maintain their temperature equilibrium. The rectal temperature increased steadily to over 43°C in a period of from 3 to 5 hr. When restrained on a wire mesh platform by means of a neck yoke and attachment of the arms along the side of the body, the monkeys held a steady rectal temperature of about 40°C for 5 hr. At a room temperature of 29°C equilibrium of rectal temperature was maintained with both types of restraint with average heart rates over a period of 4.5 hr. of 254 for one type and 255 for the other. It is concluded that the manner in which a monkey is restrained can modify its physiological responses during exposure to heat stress. (Author's summary)

363. Freedman, D. G. Constitutional and environmental interactions in rearing of four breeds of dogs. *Science* 127: 585–6 (Mar. 14), 1958.

Litters of Shetland sheep dogs, basenjis, wire-haired fox terriers and beagles were weaned at age of 3 wk. and equal members of each group were either indulged or disciplined twice daily for 15 min. over two separate periods. At the age of 8 wk. and again after the 2nd period each pup was subjected to certain tests. The scores of all indulged animals in both series differed significantly from their disciplined counterparts, the indulged ones being more active and vocal, less timid but more easily inhibited with punishment. Indulgence consisted of encouraging a pup in any activity it initiated, such as play, aggression, climbing on the supine handler, and not punishing it.

364. Friedman, S. M., Friedman, C. L. and Nakashima, M. Effects of aldosterone on blood pressure and electrolyte distribution in the rat. *Am. J. Physiol.* 195: 621–7 (Dec.), 1958.

The following data are given for normal adult male albino rats of an inbred Wistar strain: blood pressure (mm Hg) systolic

111±6, diastolic 63±3; extracellular fluid volume (ml/100 gm) 21.4±0.4; Na and K concentration (mEq/l) 140±1.4, and 4.2±0.10; extracellular Na and K (mEq/100 gm) 2.99±0.07 and 90±3.

365. Geiger, E., Human, L. E. and Middleton, M. J. Nitrogen content of gastrointestinal tracts of rats during absorptive period. *Proc. Soc. Exptl. Biol. Med.* 97: 232–4 (Jan.), 1958.

Adult male albino rats of the Wistar strain were trained to eat definite quantities of different proteins or other test meals and the N present in the gastrointestinal contents was determined at intervals following ingestion.

366. Ghadially, F. N. Effect of trauma on growth of hair. *Nature* 181: 993 (Apr. 5), 1958.

Simple mechanical trauma such as scratching or cutting the rabbit skin causes a sudden hair growth around the site of injury. It is known that hair replacement in the mouse, rat and rabbit occurs in cyclical waves of active growth while in the guinea pig and in man no gross hair growth cycle exists.

367. Goodyer, A. V. N., Mattie, L. R. and Chetrick, A. Renal response to nonshocking hemorrhage: the role of intrarenal shunts. *Am. J. Physiol.* 193: 360-4 (May), 1958.

Changes of renal red cell volume, renal plasma volume, renal hematocrit and relative renal hematocrit, in normal dogs and following isobaric hemorrhage, were determined.

368. Grauwiler, J., Spörri, H. and Wegmann, H. Zur graphischen Ermittlung des systolischen und diastolischen Blutdruckes bei Haustieren mittels des Infratonmikrophons und Druckmarkengebers von Brecht und Boucke. (Graphical recording of systolic and diastolic blood pressure in animals by the infratonmicrophone and pressure indicator of Brecht and Boucke.) *Schweiz. Arch. Tierheilk.* 100: 297–318, 1958.

The blood pressure was measured with the apparatus of Brecht and Boucke. This device consists of an inflatable cuff connected to a mercury manometer and a special microphone replacing auscultation by stethoscope. Blood pressure measurements made on horses, cattle, pigs and dogs are tabulated.

369. Great Britain, Committee of the Privy Council for Agricultural Research. *Report of the Agricultural Research Council for the year* 1956–7. London, H. M. Stationery Office, 1958, 152 pp.

Studies described in this report concern mainly livestock. On page 115–6 experiments are reported concerning the transmission of immunity from mother to young in tame rabbits: The young animal derives its immunity to disease from the mother. Antibodies produced by the mother are transmitted to the young animal either before or after birth or both. They belong to the β-globulin fraction of the circulating serum proteins. Their transmission before birth, as in man, rabbit, guinea pig, rat and mouse, involves the transport of these large protein molecules across the fetal membranes without losing their specific biological activity. Their transmission after birth, as in ruminant, pig, horse, rat and mouse, involves secretion in the colostrum or milk and transport from the alimentary tract to the circulation of the suckling.

370. Gustafsson, B. E. and Laurell, C. B. Gamma globulins in germfree rats. *J. Exptl. Med.* 108: 251–8 (Aug.), 1958.

The electrophoretic fractions of serum proteins were studied up to the fifth generation in a colony of germfree rats. The germfree animals had significantly lower concentrations of β- and γ-globulins, while the other fractions were within normal limits. (From author's summary)

371. Harvey, D. G. The measurement of oxygen consumption in small animals. *J. Pharm. and Pharmacol.* 10: 483–92 (Aug.), 1958.

The apparatus described and illustrated can be employed for the measurement of the oxygen consumption of 1–6 small animals in the weight range of 25–500 gm. The normal oxygen consumption of mice, rats and guinea pigs at 25°C has been determined. It was shown experimentally that for the assay of metabolic stimulants the guinea pig is more suitable than rats or mice.

372. Hausberger, F. X. and Hausberger, B. C. Effect of insulin and cortisone on weight gain, protein and fat content of rats. *Am. J. Physiol.* 193: 455–60 (June), 1958.

Data are reported of average protein and fat content and gain of body weight in male Wistar rats.

373. Hendrikx, A. and Epstein, F. H. Effect of feeding protein and urea on renal concentrating ability in the rat. *Am. J. Physiol.* 195: 539–42 (Dec.), 1958.

Prior feeding of male Sprague-Dawley rats with urea or protein increases the ability of the kidneys to concentrate the urine to such a degree that net losses of water are not greater after a high-nitrogen diet than after a low-protein diet. In dehydrated rats, this prior feeding evidently enables adaptation to the added load of solutes requiring urinary excretion by conserving water more efficiently.

374. Huggins, R. A., Deavers, S. and Smith, E. L. Changes in circulating plasma and proteins following graded transfusions in the dog. *Am. J. Physiol.* 193: 581–3 (June), 1958.

A series of dogs was anesthetized with a morphine-pentobarbital combination and the plasma volume measured with radioactive I^{131} and plasma protein by the method of Barbour and Hamilton. Blood was then transfused in 10 cc/kg increments up to a total of 50 cc/kg. After each 10 cc/kg of blood 20 min. was allowed for equilibration and then plasma volume and protein were redetermined. No loss of plasma volume or protein occurred with a transfusion of 10 cc/kg, but the loss of both was statistically significant with 20 cc/kg. There was a progressive loss of both plasma volume and protein from the initial values with each additional increment of 10 cc/kg. (Author's summary)

375. Hummel, K. P. Accessory adrenal cortical nodules in the mouse. *Anat. Record* 132: 281–95 (Nov.), 1958.

Accessory nodules of cortical tissue were found in 50% of the inbred mice examined and in a much lower proportion of the hybrids. In mice of strains C57L, C58 and BALB/c there were incidences higher than 50%; in mice of strains C57BL/6, DBA/1, RIII and CE incidences of approximately 50%; and in mice of strains A and C3H incidences of less than 50%. In all strains, incidences were proportionally higher in females than in males. In strains C57L and C3H, incidences were proportionally higher in adults, and in strains C58, BALB/c and A, incidences were proportionally higher in weanling mice. The strain, sex and age differences can not be correlated with other known differences in these strains of mice. (Condensed from author's summary)

XUM

376. IGLESIAS, R. AND MARDONES, E. Spontaneous and transplantable functional tumor of the adrenal cortex in the A × C rat. *Brit. J. Cancer* 12: 20–7 (Mar.), 1958.

The following tissue weights (mg) are reported for normal A × C rats: males 302–438 days of age, gonads right 963±167, left 1127±88, right seminal vesicle 365±48; females 86–428 days of age, gonads right 30±1.6, left 32±2.9. The incidence of a spontaneous metastasizing and transplantable tumor of the suprarenal cortex, found in a noncastrated female rat of the A × C strain is described.

377. JACOBS, B. B. Variations in thyroid morphology of mice. *Proc. Soc. Exptl. Biol. Med.* 97: 115–8 (Jan.), 1958.

Observations of thyroid follicle epithelial heights and diameters were analyzed with respect to age and parity in C3H and C57 mice. Epithelial heights decreased and follicle diameters increased with aging and breeding. The presence of tumors in the C3H parous females was associated with decreased epithelial height and increased diameter of the thyroid follicles as compared to nontumor-bearing mice of corresponding ages. These changes suggest that aging, breeding and the presence of tumor are associated with decreased thyroid function. (Author's summary)

378. JOHNSON, E.: Quantitative studies of hair growth in the albino rat. I. Normal males and females. II. The effect of sex hormones. III. The role of the adrenal glands. *J. Endocrinol.* 16: 337–68 (Apr.), 1958.

I. The patterns of the 1st and 2nd hair growth waves, forming the 2nd and 3rd coats, were followed in albino rats which had been dyed black before the start of hair growth. The length of hair produced during the growth waves varies from region to region of the body. These regional differences are partly the result of differences in rates of growth, but mainly due to differences in the duration of the period of follicular activity. The duration of the growing and resting periods varies in different areas of the body. In female rats the growth wave moves more slowly, the definitive length of hair is shorter, and the loss of club hairs is slower than in the male.

II. Spaying of female rats and castration of males, each 7 wk. of age, accelerated the passage of the 2nd wave of hair growth.

III. Adrenalectomy 2 wk. before the start of the 2nd wave of hair growth advanced the beginning of the wave in female rats, and speeded its passage over the body in both males and females. Adrenalectomy after the wave of hair growth had begun was less effective. (Condensed from author's summary)

379. JOHNSON, H. D., CHENG, C. S. AND RAGSDALE, A. C. Environmental physiology and shelter engineering with special reference to domestic animals. XLVI. Comparison of the effect of environmental temperature on rabbits and cattle. Part 2. Influence of rising environmental temperature on the physiological reactions of rabbits and cattle. *Missouri Univ. Agr. Expt. Sta. Research Bull.* No. 648, Jan., 1958, 27 pp.

Two groups of New Zealand rabbits were raised at 48° and 83°F, respectively, and then subjected to different environmental temperatures, increasing gradually from 48° to 110°F. At each environmental temperature level the following data were determined: rectal, skin and hair temperatures; total, respiratory and surface vaporization; heat production; pulse and respiration rate; thyroid I^{131} activity; feed and water consumption; body weight; urine and feces moisture loss. Similar data were obtained for cows. The methods used in obtaining these data are reported.

380. KAY, H. AND BIRREN, J. E. Swimming speed of the albino rat: II. Fatigue, practice, and drug effects on age and sex differences. *J. Gerontol.* 13: 378–85 (Oct.), 1958.

Large differences were encountered in the rate at which older and younger groups of Sprague-Dawley rats fatigued during the course of 30 swimming trials and these performances could be subsequently improved with repeated practice. Experiments to study the effect of different drugs on swimming performance of the rats were inconclusive.

381. KENNEDY, G. C., PEARCE, W. M. AND PARROTT, D. M. V. Liver growth in the lactating rat. *J. Endocrinol.* 17: 158–60 (July), 1958.

During the 2nd and 3rd weeks of lactation the liver of the rat hypertrophied to approximately twice its normal size. There was a smaller, but significant, increase in the deoxyribonucleic acid (DNA) content, indicating an increase in cell number. The increase in liver protein was reversible, but that in DNA was not. These effects appeared to be due to changes in the intake of food. (Author's summary)

382. KNILL, L. M., PODLESKI, T. R. AND CHILDS, W. A. Normal values of swine serum proteins. *Proc. Soc. Exptl. Biol. Med.* 97: 224–6 (Feb.), 1958.

Zone electrophoretic examination of sera from a large, random selection of apparently healthy hogs has yielded statistically valid protein concentrations. Under the conditions of this experiment, only albumin, α-, β-, and γ-globulin were resolved and quantitated. The "f" fraction (11) and α_1-globulin are discernible only under specific conditions. The ionic strength, the pH of the buffer and apparently the separating medium influence the resolution of the "f" and α_1 fractions. (Author's summary)

383. KRISE, G. M., JR. AND WALD, N. The normal blood picture of the *Macaca mulatta* monkey. *U. S. Air Force, School of Aviation Medicine Rept.* 57–130 (July), 1957; also *J. Appl. Physiol.* 12: 482–4 (May), 1958.

Over a period of 2 yr. 538 male *Macaca mulatta* monkeys, age from 30 to 42 mo., weight from 4 to 13 lb., were examined for the following hematologic measures: hemoglobin, red blood cell count, white blood cell count, differential white blood cell counts, reticulocytes, sedimentation rates, hematocrit, platelet count, bilobed lymphocyte count, plasma prothrombin time, serum prothrombin time, Lee-White clotting time, and onset and rate of clot retraction. The mean, range, standard deviation, and number of analyses are given for each measurement. Results are compared with existing data found in the literature. (Author's summary)

384. MCCLURE, T. J. Temporary nutritional stress and infertility in mice. *Nature* 181: 1132 (Apr. 19), 1958.

Short periods of starvation at or about the time of mating can be detrimental to the fertility of mice but the residual effect of starvation is short.

385. MEFFERD, R. B., JR. AND HALE, H. B. Effects of altitude, cold and heat on metabolic interrelationships in rats. *Am. J. Physiol.* 193: 443–8 (May), 1958.

Adult male Wistar rats were exposed for 3 mo. to simulated altitude (18,000 ft.) or to hot or cold environments (5°, 25° or 35°C). During the final month comparisons were made concerning body weight, food and water intake, 24-hr. fasting urine volume, and excretion of Na, K, PO_4, Mg, Ca, urea, uric acid, and amino acids.

386. MEFFERD, R. B., JR. AND HALE, H. B. Effects of abrupt temperature changes on excretion characteristics of rats acclimated to cold, neutral or hot environments. *Am. J. Physiol.* 195: 726–34 (Dec.), 1958.

The responses of acclimated rats (heat, 35°C; neutral, 24°C; or cold, 3°C) to abrupt temperature changes (24-hr. exposure with fasting) are compared. Variables studied include weight loss, water intake, urine volume, urinary Na, K, Ca, Mg, PO_4, urea, uric acid, amino acids. (Condensed from author's summary)

387. MEFFERD, R. B., JR. AND HALE, H. B. Effects of thermal conditioning on metabolic responses of rats to altitude. *Am. J. Physiol.* 195: 735–8 (Dec.), 1958.

The metabolic responses of rats acclimated to different temperatures (3°, 24° and 35°C) were compared during a 24-hr. fasting exposure to low barometric pressure (380 mm Hg). Determinations included fasting weight loss, water intake, urine volume and urinary excretion of Na, K, Mg, Ca, PO_4, urea, uric acid, creatinine, creatine, taurine, β-alanine, glycine, α-alanine, valine + methionine, serine, threonine, tyrosine, glutamic acid, aspartic acid, lysine, arginine and histidine. (Condensed from author's summary)

388. MEFFERD, R. B., JR., HALE, H. B. AND MARTENS, H. H. Nitrogen and electrolyte excretion of rats chronically exposed to adverse environments. *Am. J. Physiol.* 192: 209–18 (Jan.), 1958.

Urinary excretion patterns of adult male Wistar rats exposed for 11 wk. to control (25°C) or to adverse conditions (5°C, 35°C), or simulated altitude (equivalent to 18,000 ft.) were determined using 24-hr fasting urine specimens collected weekly during the final 4 wk. Relative to metabolic body weight, fasting water intake tended to vary directly with temperature, but urinary Na, K, Mg, Ca, PO_4, urea, valine and alanine tended to vary inversely with temperature. Creatinine, uric acid, histidine, glycine, serine, methionine, glutamic acid and aspartic acid excretion tended to vary nonlinearly with temperature. Altitude induced reductions in the majority of the urinary constituents. (Author's abstract)

389. MEFFERD, R. B., JR., NYMAN, M. A. AND WEBSTER, W. W. Whole body lipid metabolism of rats after chronic exposure to adverse environments. *Am. J. Physiol.* 195: 744–6 (Dec.), 1958.

Specific activities of the total nonsaponifiable lipids, cholesterol, total fatty acids, solid fatty acids and liquid fatty acids, and the liver succinic dehydrogenase activities were determined for adult male Sherman strain rats following chronic exposure (2 mo.) to cold (2°C), neutral (24°C), or hot (35°C) environments or to discontinuous (4 hr. daily) simulated altitude (18,000 ft., 24°C). (Condensed from author's summary)

390. MICHAEL, R. P. Sexual behaviour and the vaginal cycle in the cat. *Nature* 181: 567–8 (Feb. 22), 1958.

Patterns of sexual behavior shown by 30 reproductively active female cats were studied over 2 yr. Behavioral characteristics were recorded for each of the four stages of the cycle. The relationship between behavior and cytology of the vaginal smear was studied in 340 mating tests.

391. MÖBEST, H. AND TOLKI, R. Über das Vorkommen komplementbindender, praeformierter Antikörper in normalen Kaninchenseren. (Presence of complement-fixing, preformed antibodies in normal rabbit serum.) *Zentr. Bakteriol. Parasitenk. Abt. I. Orig.* 173: 472–8 (Dec.), 1958.

Serum of untreated rabbits at the age of puberty was found to show a positive parotitis and a positive psittacosis complement-binding reaction. It contained also complement-binding antibodies against toxoplasmosis.

392. MURAYAMA, M. Titratable sulfhydryl groups of horse, sheep, dog, and cow hemoglobins at 0° and 38°. *J. Biol. Chem.* 233: 594–6 (Sept.), 1958.

Amperometrically titratable sulfhydryl groups of electrodialyzed hemoglobins of horse, sheep, dog, and cow have been investigated with argentometric and mercurimetric methods at 0° and 38°C. The results obtained support previous views that there is a close relationship between the genetics of an individual organism and the kind of protein it produces and that the heterogenicity of hemoglobins may in part be due to the conformational differences of the peptide chains which are reflected in the conformational differences of —SH groups.

393. NALBANDOV, A. V. *Reproductive Physiology. Comparative Reproductive Physiology of Domestic Animals, Laboratory Animals and Man.* San Francisco, Freeman, 1958, 271 pp.

The biology of sex; structure of male and female reproductive systems; endocrinology of reproduction; reproduction in female mammals and birds; follicular growth, ovulation, formation of corpora lutea; some chemical and physiological properties of hormones; reproduction in male mammals and birds; germ cells; young embryo; efficiency of reproduction; pregnancy, parturition, and lactation; fertility and sterility.

394. NATIONAL RESEARCH COUNCIL, COMMITTEE ON THE HANDBOOK OF BIOLOGICAL DATA. *Handbook of Respiration*, edited by D. S. DITTMER AND R. M. GREBE. Philadelphia, Saunders, 1958, 403 pp.

The book contains tables arranged according to the following classifications: Basic physical and chemical data; basic respiratory anatomy; lung volumes and pulmonary function; blood respiratory characteristics; erythrocytes and respiratory pigments; mechanics of breathing; artificial respiration; effects of exercise and of various concentrations of inhaled gases; other factors affecting respiration; O_2 consumption; respiration of tissues. Animals included in the survey are cat, dog, guinea pig, rabbit, rat, monkey, frog and others.

395. NOYES, R. W., ADAMS, C. E. AND WALTON, A. Transport of spermatozoa into the uterus of the rabbit. *Fertility and Sterility* 9: 288–99 (July–Aug.), 1958.

Neither radiopaque media nor semen normally pass from the vagina into the uterus during copulation or following artificial stimulation of the vulva. Living spermatozoa pass through the cervical barrier as the result of their own motility, but the exact point at which their rate of progress is first influenced by muscular contractions of the genital tract has not yet been established. (From author's summary)

396. PARKES, A. S. Suspended animation. (Foreign Letters.) *J. Am. Med. Assoc.* 168: 1152 (Oct. 5), 1958.

Long-term preservation of living cells by freezing was studied. Rats, mice and dogs could be revived after being cooled to 32°F

and after heart beat and respiration had been arrested for 1 or 2 hr. Golden hamsters could be resuscitated undamaged after cooling to 23°F or freezing to the extent of crystallizing 50% of its body water.

397. PITTAWAY, E. M. Blood for transfusions in dogs. First Annual Congress of British Small Animal Vet. Assoc. at London, England, 1958.

In dogs there are at least five distinct blood groups: A, B, C, D, and E. It is only the A factor which causes concern; groups B, C, D, and E seem to produce no antibody likely to cause a great deal of trouble on transfusion. An initial transfusion causes little trouble, as strong isoagglutinins do not occur naturally. It is only after the patient has been sensitized by an initial transfusion that reactions occur. An anti-A producing factor is present in approximately 60% of random dogs and is obviously significant where continuous transfusion is contemplated. It is important to impress upon the owners of transfused dogs that they should not have a subsequent transfusion elsewhere without warning the veterinary surgeon in charge. (*J. Am. Vet. Med. Assoc.* 134: 513 (June 1), 1959.)

398. RIEDESEL, M. L. AND FOLK, G. E., JR. Serum electrolyte levels in hibernating mammals. *Am. Naturalist* 92: 307–12 (Sept.–Oct.), 1958.

Serum Ca and K measurements are recorded for 4 species of hibernating animals, including 2 species of bats, hamsters and thirteen-lined ground squirrels.

399. RIOPELLE, A. J. Behavior of primate individuals and groups. *U. S. Army Med. Research Lab. Rept.* No. 334, Aug. 18, 1958, 8 pp.

A study of the behavioral characteristics of several genera of primates showed that the social patterns of Old World monkeys differ markedly from those of New World monkeys. Equally different intellectual patterns are discernible. Tests used for determining behavioral capacity were the delayed response test, the instrumentation test and tests involving discrimination.

400. ROSA, J., SCHAPIRA, G., DREYFUS, J. C., DE GROUCHY, J., MATHÉ, G. AND BERNARD, J. Different heterogeneities of mouse haemoglobin according to strains. *Nature* 182: 947–8 (Oct. 4), 1958.

By means of starch gel electrophoresis, 4 types of hemoglobin patterns were identified in 6 inbred strains of mice. The strains were as follows: C57Bl16, C57Br, AKR, Swiss, DBA2 and C3H.

401. RUSSELL, E. S. AND GERALD, P. S. Inherited electrophoretic hemoglobin patterns among 20 inbred strains of mice. *Science* 128: 1569–70 (Dec. 19), 1958.

Mice from 6 inbred strains (C57BL/6, C57BR/cd, C57L/He, C58, SWR, and WK) carried single type hemoglobin, and mice from 14 inbred strains (A/He, A/Jax, AKR, BALB/c, C3H/Jax, C3HeB, DBA/1, DBA/2, MA/My, RFM, 129, WB, WC, and WH) carried diffuse-type hemoglobin. Mice with either type of hemoglobin appear to be normal and healthy, and both alleles must have been present in wild mice to account for the observed strain distribution. (From author's summary)

402. SAINTE-MARIE, G. AND LEBLOND, C. P. Tentative pattern for renewal of lymphocytes in cortex of the rat thymus. *Proc. Soc. Exptl. Biol. Med.* 97: 263–70 (Feb.), 1958.

Counts of resting and dividing cells in the cortex of the thymus of 10-wk.-old male rats reveal a high mitotic index of the 4 cell types present: reticular cells, large, medium and small lymphocytes. This observation indicates that each one of the 4 cell types is being renewed. Presumably this renewal yields lymphocytes which leave the thymus and enter the circulation. From the mean numbers of cells and of mitoses and the mean mitotic indices of the 4 cell types over a 24-hr. period, a tentative scheme referred to as "stem cell renewal theory" is presented to account for the continuous production of lymphocytes in the thymus. (Condensed from author's summary)

403. SCHERMER, S. *Die Blutmorphologie der Laboratoriumstiere.* (*The Blood Morphology of Laboratory Animals.*) 2nd ed., Leipzig, J. A. Barth, 1958, 186 pp.

A special chapter is devoted to each of the following 12 laboratory animals: rabbit, guinea pig, white rat, white mouse, golden hamster, dog, cat, sheep, monkey, chicken, pigeon and frog. After a short discussion on maintenance and nutrition, the blood collecting technique for each animal is described and data are given for blood constituents (red and white cells, neutrophils, eosinophils, basophils, lymphocytes, monocytes), physical properties of the blood (coagulation time, sedimentation rate, viscosity), blood sugar and albumin content, lipoid and mineral content of the serum and composition of the cells of the bone marrow.

404. SELLERS, A. F., PRITCHARD, W. R., WEBER, A. F. AND SAUTTER, J. H. Renal function studies on normal dairy cattle and those with postparturient albuminuria. *Am. J. Vet. Research* 19: 580–4 (July), 1958.

Renal function data are reported for normal and paretic dairy cattle. Blood and pulse pressure, changes of the blood cells and the appearance of the adrenals were studied in paretic animals.

405. SHREWSBURY, M. M. Rate of flow and cell count of thoracic duct lymph in the mouse. *Proc. Soc. Exptl. Biol. Med.* 99: 53–4 (Oct.), 1958.

A method is described for obtaining lymph from the abdominal thoracic duct of the anesthetized mouse. Data are presented on rate of flow, white cell count and total lymphocyte output of the lymph obtained.

406. SPRAY, G. H. AND TAYLOR, K. B. Vitamin B_{12} activity in the serum of the rat. *Nature* 182: 1309–10 (Nov. 8), 1958.

Vitamin B_{12} activity was determined in Wistar albino rats by using *Lactobacillus leichmannii* as test organism. Results obtained in normal and gastrectomized rats and rats kept on a vitamin B_{12}-deficient diet are tabulated. Estimation of vitamin B_{12} activity is useful in deciding whether or not an animal is deficient in vitamin B_{12}.

407. STAATS, J. Behaviour studies on inbred mice: a selected bibliography. *Animal Behaviour* 6: 77–84 (Jan.–Apr.), 1958.

The bibliography of 196 references has been compiled from the Subject-Strain Bibliography. The orientation of this limited bibliography is to the strain of mice rather than to the field of behavior; it includes also pharmacological studies in which the end point is some activity of the mouse.

408. STEWART, P. B. AND BURGEN, A. S. V. The turnover of fluid in the dog's pleural cavity. *J. Lab. Clin. Med.* 52: 212–30 (Aug.), 1958.

The factors responsible for the movement of fluid, solutes and cells into and out of the pleural cavity were studied quantitatively.

The average volume of pleural fluid in the dog was found to be 1.3 ml, its average protein concentration 1.39 gm/100 ml, its red blood cell count 6,300/cu mm and its white blood cell count 2,820/cu mm.

409. STREICHER, E. Age changes in the calcium content of rat brain. *J. Gerontol.* 13: 356–8 (Oct.), 1958.

The Ca content of the brain was measured in 37 Sprague-Dawley rats, 2.5–33 mo. old. The following average values (mEq/kg) were found for age groups 2.5–4, 12, 22–28, 30–33 mo.: 5.2, 12.2, 9.1, 9.3, respectively. Large individual variations were observed in each age group and the two halves of the same brain often differed markedly from each other. (15 references)

410. STRONG, L. C. AND FULLER, C. A. Maternal age at time of first litters in mice. *J. Gerontol.* 13: 237–40 (July), 1958.

Based on observation of 1751 female mice belonging to one or the other of 5 separate descents between the F_1 and F_{12} generations of inbreeding, the earliest maternal age at time of first litter was 38 days; the latest, 318 days. The original strain was the Strong polydactylous (many-toed).

411. THOMPSON, W. R. AND HIGGINS, W. H. Emotion and organized behaviour: Experimental data bearing on the Leeper-Young controversy. *Can. J. Psychol.* 12: 61–7 (June), 1958.

Albino rats of the Sherman strain were habituated to a particular place, a black or white compartment. When given an electric shock, they tended to choose their familiar compartment, while nonshocked rats escaped into the new compartment. Activity level of shocked animals was lower than that of controls; autonomic activity and stability of activity was greater.

412. WANG, C., PARONETTO, F., SOHAR, E. AND ADLERSBERG, D. Effects of ethionine administration in rabbits and dogs. I. Changes in serum proteins, lipids, lipoproteins, and glycoproteins and in blood coagulation. *A.M.A. Arch. Pathol.* 65: 279–85 (Mar.), 1958.

Control data are given for serum lipids, serum proteins, blood sugar, lipoproteins, glycoproteins and serum amylase levels in "gray chinchilla" rabbits and mongrel dogs. The serum-, lipo-, and glycoproteins were studied by paper electrophoresis.

413. WEIL, A. J. AND FINKLER, A. E. Antigens of rabbit semen. *Proc. Soc. Exptl. Biol. Med.* 98: 794–7 (Aug.–Sept.), 1958.

The immunological relationship between spermatozoa and seminal plasma was studied in Dutch belted rabbits and particular emphasis was laid on the search for the site of production of these antigens.

414. WELLERS, G. Un dispositif simple en vue de l'étude du bilan du soufre chez le rat. (A simple arrangement for the study of the sulfur balance in the rat.) *J. Physiol. (Paris)* 50: 565–7 (Mar.), 1958.

A metabolism cage is described which permits the determination of the S balance in the rat. The S balance of a female adult rat on various diets was determined.

415. WELLING, W. AND VAN BEKKUM, D. W. Different types of haemoglobin in two strains of mice. *Nature* 182: 946–7 (Oct. 4), 1958.

Two methods are described for the identification of hemoglobin patterns, i.e. agar gel electrophoresis and denaturation with alkali. Hemoglobin of C57BL mice was found to have only one component, hemoglobin of CBA had two and that of the hybrid F_1 did not show a sharp boundary. For the identification of the type of hemoglobin in CBA-C57BL chimera the electrophoretic technique was preferable because of its simplicity.

416. YEN, H. C. Y., STANGER, R. L. AND MILLMAN, N. Isolation-induced aggressive behavior in ataractic tests. *J. Pharmacol. Exptl. Therap.* 122: 85A (Jan.), 1958.

After being isolated in a cage for 2–3 wk. normal male mice developed an aggressive behavior. The criterion for aggressiveness was the immediate attack by such isolated mice upon normal, nonisolated mice.

417. ZANGWILL, O. L. Psychology of laboratory animals. Letter to the Editor. *Lancet* 2: 851 (Oct. 18), 1958.

Rats have been used in many psychological experiments providing information in regard to motivation and learning. The author points out that ethological studies should be made to obtain information on the social and territorial organization of rat colonies in the wild and in captivity.

418. ZOMZELY, C. AND MAYER, J. Levels of serum cholesterol in obese mice. *Nature* 182: 1738–9 (Dec. 20), 1958.

Serum cholesterol levels were determined by the Kendall-Abell method in the following four types of obese mice and normal controls: *1*) hypothalamic-Swiss controls; *2*) hyperglycemic-V-stock; *3*) adrenocorticotrophic hormone-LAF; *4*) yellow-black controls. It appears that obese mice of different types suitably compared may offer good material for studies of serum cholesterol and atherosclerosis.

419. BARTLETT, R. G., JR. Effects of restraint on oxygen consumption of the cold exposed guinea pig. *J. Appl. Physiol.* 14: 46–8 (Jan.), 1959.

The oxygen consumption of cold-exposed, restrained guinea pigs is significantly greater than that of cold-exposed, nonrestrained controls. Similar observations have been made for the rat. (Condensed from author's abstract)

420. BARTLETT, R. G., JR. AND ALTLAND, P. D. Effect of restraint on altitude tolerance in the rat. *J. Appl. Physiol.* 14: 395–6 (May), 1959.

Young adult Sprague-Dawley rats were exposed to a simulated altitude of 33,500 ft. at ambient room temperature of 22°–24°C. Rats which were restrained by maintenance in loosely fitting wire mesh cylinders closed at both ends died significantly sooner than nonrestrained controls under the same conditions.

421. BARTLETT, R. G., JR. AND ALTLAND, P. D. Relation of body temperature and restraint to altitude tolerance in the rat. *J. Appl. Physiol.* 14: 785–8 (Sept.), 1959.

Sprague-Dawley rats restrained by loosely fitting wire mesh cylinders immediately before altitude exposure (33,500 ft.) with rapid ascent (2,000 ft/min) died significantly sooner than nonrestrained controls. Slow stepwise ascent over 2.5–4 hr. increased the altitude tolerance of both restrained and unrestrained rats, but much more for the restrained animals. When body temperatures were dropped to 25°C before altitude exposure, no deaths (up to 6 hr.) occurred in either the restrained or unrestrained rats. The conclusion was drawn that, depending on the experimental procedure, restraint may increase or decrease altitude tolerance.

XUM

422. BARTLETT, R. G., JR. AND YOUNG, M. W. 'Free roaming' in the albino rat and its effect on restraint hypothermia. *J. Appl. Physiol.* 14: 393–4 (May), 1959.

When young adult Sprague-Dawley rats were given the run of the laboratory their resistance to exposure to cold while being housed in individual cages increased. Changes which may occur in the "free-roaming" rat causing this phenomenon are discussed.

423. BENNETT, H. S., LUFT, J. H. AND HAMPTON, J. C. Morphological classifications of vertebrate blood capillaries. *Am. J. Physiol.* 196: 381–90 (Feb.), 1959.

Morphological features of blood capillaries obtained by electron microscopy from various vertebrate forms and organs of rats and mice are presented. Simple classifications are proposed, based on presence or absence of continuous basement membrane, on the nature of the endothelial cell and on the presence or absence of a complete investment of pericapillary cells. (Author's summary modified)

424. BERING, E. A., JR. Cerebrospinal fluid production and its relationship to cerebral metabolism and cerebral blood flow. *Am. J. Physiol.* 197: 825–8 (Oct.), 1959.

Cerebrospinal fluid was obtained from mongrel dogs by percutaneously puncturing the cisterna magna and allowing the fluid to flow through an attached tube. Cerebral blood flow and O_2 consumption were measured by the NO method of Kety and Schmidt. Mean data for a normal dog per 100 gm brain/min. were found as 66 cu mm and 3.3 cc, respectively.

425. BLUMER, W. F. C. AND COLE, J. Various degrees of hypothermia in mice. *J. Appl. Physiol.* 14: 987–9 (Nov.), 1959.

Some mice were cooled to a deep body temperature of 15°C, others in ice for an additional 20 min. to 1°C, still others in ice for 45 min. to 1°C. The function of the central nervous system was tested by a modification of the revolving bar method. The results inferred that duration as well as intensity of hypothermia is significant and that a critical point is reached after 20 min. in ice. Histology revealed no CNS damage. (From author's summary)

426. BOATMAN, J. B., WALSH, J. M., EPSTEIN, L. I. AND RABINOVITZ, M. J. Fluid and electrolyte changes of thyroidectomized rats in a cold environment. *Am. J. Physiol.* 196: 1214–7 (June), 1959.

Body weight, urine volume and water consumption of groups of normal rats at ordinary temperature and after exposure to a cold environment for 10 days are reported.

427. BRACHET, J. AND MIRSKY, A. E., ed. *The Cell. Biochemistry, Physiology, Morphology.* Vol. 1. New York, Academic Press, 1959, 816 pp.

The book contains the following chapters: Optical methods in cytology; fixation and staining; autoradiography; quantitative microscopical techniques for single cells; quantitative microchemical techniques of histo- and cytochemistry; micrurgical studies on living cells; isolation of subcellular components; the cell as organism, "tissue culture," cellular autonomy, and cellular interrelations; fertilization; sex determination; differentiation of vertebrate cells; patterns of cell growth and differentiation in plants; nucleocytoplasmic interactions in eggs and embryos; acquisition of biological specificity; effects of radiations on cells.

428. BRADLEY, O. C. *Topographical Anatomy of the Dog.* 6th ed. New York, Macmillan, 1959, 332 pp.

The book contains the following chapters: Abdomen, thorax, pelvic limb, pelvis, thoracic limb, head and neck, lymphatic system.

429. BRAMANTE, P. O. Apparatus for automatically recording oxygen consumption, respiratory movements and activity of small animals. *J. Appl. Physiol.* 14: 1063–5 (Nov.), 1959.

An apparatus is described which, by means of electronic transduction and amplification, permits the continuous recording of O_2 consumption as well as the tracing of several respiratory characteristics (rate, depth, rhythm, etc.) of the animal together with its spontaneous activity. Tracings obtained for 3 rats are illustrated.

430. BRIZZEE, K. R. AND VITALE, D. Functional development of the emetic apparatus in the cat. *Am. J. Physiol.* 196: 1189–90 (June), 1959.

Emetic tests were carried out with graded doses of lanatoside C (Cedilanid) from 0.06–0.8 mg/kg intravenously and total body x-irradiation at a dose level of 12,000 roentgens. The cats were grouped in developmental stages according to weight, from 50 gm to 2–3 kg. The period between the 150–250 gm stage was found as the critical period in the development of the emetic stages for the 2 stimuli employed. The decrease in the incidence of vomiting in early age groups at the various dose levels of lanatoside indicated that the mechanism is less sensitive in younger animals than in older groups.

431. BROOKRESON, A. D. AND TURNER, C. W. Normal growth of mammary gland in pregnant and lactating mice. *Proc. Soc. Exptl. Biol. Med.* 102: 744–5 (Dec.), 1959.

Using desoxyribonucleic acid as index of mammary gland growth a study of changes from virgin throughout pregnancy and lactation in Webster-Swiss mice was conducted. It was found that only 30.6% of total growth occurred during the first 12 days of pregnancy, 45.7% in the latter half of pregnancy and 21.9% from parturition to the 14th day of lactation.

432. BURKE, W. T. AND HARRIS, C. Total cell counts of the bone marrow of normal albino rats from 1 to 50 weeks of age. *Blood* 14: 409–14 (Apr.), 1959.

A method is described by which the total nucleated cell count of femoral bone marrow of the rat can be estimated and cell population expressed in terms of differential counts. Normal values of total nucleated cell counts and the cellular distributions are given for 7 age groups. These data indicate considerable change in bone marrow total cell population in rats 1–10 wk. of age. (Author's summary)

433. CALLAHAN, A. B., DEGELMAN, J. AND LUTZ, B. R. Systolic blood pressure in the hamster as determined by a strain-gauge transducer. *J. Appl. Physiol.* 14: 1051–2 (Nov.), 1959.

The systolic blood pressure was measured in the hamster (*Mesocricetus auratus*), using the return of flow in the hind foot, as indicated by a strain-gauge transducer, after occlusion of the leg vessels by a cuff. The method also indicates the pulse return and records continuous respiration and pulse rate. The measurements were taken during anesthesia with Nembutal sodium. Simultaneous determination of the systolic blood pressure in 20 hamsters by carotid cannulation and strain-gauge manometry gave average values of 98.4 and 97.8 mm Hg, respectively. In 28 normal unoperated hamsters an average figure of 109.5 mm Hg was found by the strain-gauge method.

434. CARR, M. H. AND SCHLOERB, P. R. Blood components in the dog: Normal values. *J. Lab. Clin. Med.* 53: 646–52 (Apr.), 1959.

Analytical data for the various blood components in dogs were gathered over a period of several years and compared with values for human subjects. The following were determined: serum electrolytes: Na, K, Ca, Mg, Cl, inorganic PO_4, bicarbonate, protein; nitrogenous constituents (nonprotein nitrogen, urea, creatinine); protein components (total protein, albumin, globulin); hematocrit; plasma volume, extracellular fluid.

435. CHARMS, B. L. AND ENGLE, M. Measurement of bronchial artery blood flow in intact animals. *Federation Proc.* 18: Abstr. No. 798 (Mar.), 1959.

A direct method for determining bronchial artery blood flow has been developed in dogs which may be applied to human subjects. Mongrel dogs were anesthetized lightly with Nembutal so as to breathe spontaneously on room air. The equipment used is described. Expired air from the occluded lung contained 0.3%–0.6% CO_2. Bronchial blood flow was calculated to range from 20–200 cc/min. and averaged 2% of the cardiac output.

436. CHEW, R. M. AND BUTTERWORTH, B. B. Growth and development of Merriam's kangaroo rat, *Dipodomys merriami*. *Growth* 23: 79–95 (June), 1959.

Data are presented on the growth and development of 34 individuals of 12 litters of *Dipodomys merriami* reared in captivity. A method is suggested for estimating the ages of live individuals captured in the field, based on the growth of tail.

437. CLARK, C. H. AND WOODLEY, C. H. A comparison of blood volumes as measured by rose bengal, T-1824 (Evans blue), radiochromium-tagged erythrocytes, and a combination of the latter two. *Am. J. Vet. Research* 20: 1067–8 (Nov.), 1959.

Normal blood volumes were determined in healthy dogs by using one of the following methods: T-1824, rose bengal, Cr^{51}-tagged cells, combination of T-1824 and Cr^{51}. The data obtained by these methods were 8.72%, 9.19%, 7.07% and 8.1% of the body weight, respectively.

438. COLE, H. H. AND CUPPS, P. T., ed. *Reproduction in Domestic Animals*. New York, Academic Press, 1959, 2 vols.

The books contain chapters on the following topics: I. Anatomy of the female and male reproductive organs; role of anterior pituitary gonadotropins, gonadal hormones, thyroid, adrenal and posterior pituitary hormones, and of the nervous system in reproductive processes; estrous cycle of cow, mare, ewe, doe, sow and dog; fertilization and development of the egg; implantation, development of the fetus, and fetal membranes; endocrine mechanism during pregnancy; factors affecting gestation length and parturition; mammary growth and lactation. II. Spermatogenesis and morphology of the spermatozoon; biochemistry of semen and secretions of male accessory organs; libido in the male; techniques of collection, dilution, and storage of semen; insemination techniques; nutrition and reproduction in domestic animals; environmental factors, other than nutrition, affecting reproduction; anatomical and physiological factors affecting fertility in domestic animals; infectious diseases influencing reproduction; reproduction in the domestic fowl: physiology of the female and male.

439. CORNELIUS, C. E., BISHOP, J., SWITZER, J. AND RHODE, E. A. Serum and tissue transaminase activities in domestic animals. *Cornell Vet.* 49: 116–26 (Jan.), 1959.

Glutamic-oxaloacetic and glutamic-pyruvic transaminase activities in serum and tissue were determined for normal horses, cattle, calves, swine, dogs and chickens.

440. CULVER, W. E. Effects of cold on man. An annotated bibliography, 1938–1951. *Physiol. Revs.* 39, Suppl. 3: 1–524 (Oct.), 1959.

The bibliography contains 2,736 references and an author index. The subject matter is distributed into the following major classifications: temperature regulation, resistance to cold, hypothermia, physiological effects of cold, pathological effects of cold. Effects on the various warm-blooded animals used in experimental laboratories are included.

441. DAVIS, D. L. AND HAMILTON, W. F. Small vessel responses of the rabbit ear. *Am. J. Physiol.* 196: 1312–5 (June), 1959.

Blood pressures were recorded continuously from small arteries and veins of the rabbit ear by inserting 0.1 mm outer diameter glass cannulae through the dorsal skin into the lumen of 0.3–0.5 mm diameter vessels. The cannulae did not occlude the lumen of the vessels. Mechanical occlusion of the macroscopically visible small veins enhanced the initial elevation in small vein pressure in response to stimulation of the sympathetic trunk. With reduced body temperature and the same degree of mechanical occlusion, a maintained elevation of small vein pressure occurred throughout the entire stimulation period. This can be interpreted as the result of constriction of the small vein walls upon a column of blood held static in the occluded vein. (Condensed from author's summary)

442. DAVIS, D. L. AND HAMILTON, W. F. Small vessel responses of the dog paw. *Am. J. Physiol.* 196: 1316–21 (June), 1959.

Pressures and flows were measured in small veins and arteries of the dog hind paw during stimulation of the ipsilateral lumbar sympathetic trunk. At stimulation frequencies less than 1–2/sec. the constrictor response was limited to very small arteries, or arterioles. Small artery pressure increased while small vein pressure and blood flow decreased. At higher stimulation frequencies flow stopped, and small artery pressures fell to low levels (in many experiments to values well below the plasma oncotic pressure). Closure of arteries occurred at the ankle and a static column was formed which communicated with the capillaries. Simultaneously small vein pressure rose well above the oncotic level and was long maintained. (Condensed from author's summary)

443. DAWES, G. S. AND MOTT, J. C. Reflex respiratory activity in the new-born rabbit. *J. Physiol.* (*London*) 145: 85–97 (Jan.), 1959.

A method is described for measuring tidal air in small animals without surgical interference. The respiratory movements were measured by recording the change of electrical capacity between their bodies and a brass tube in which they were placed. The tests showed that several respiratory reflexes function effectively in the newborn rabbit. They suggest that failure to maintain hyperpnea during anoxia is not necessarily related to depression of the respiratory center. (Author's summary modified)

444. DENENBERG, V. H. Learning differences in two separated lines of mice. *Science* 130: 451–2 (Aug. 21), 1959.

Significant differences in the mean conditioning score were found in 150-day-old C57BL/10 mice originating from 2 different

laboratories of the Roscoe B. Jackson Memorial Laboratory. Further trials were carried out with the 2 groups at 50 days of age. The conditioning procedure consisted essentially of presenting a 3-sec. buzzer which was always followed by 1 sec. of shock; 41 sec. later this buzzer-shock treatment was repeated. The tests confirmed the above-obtained differences of responses. Since the 2 groups had been apart for more than 15–20 generations of separate breeding, they should be considered substrains and designated as C57BL/10Jax and C57BL/10Sc. It is suggested that learning capacity and response topography in the 2 substrains has been affected by a behavioral mutation. The 2 substrains appear to be useful for experiments on the genetics of behavior.

445. DIDISHEIM, P., HATTORI, K. AND LEWIS, J. H. Hematologic and coagulation studies in various animal species. *J. Lab. Clin. Med.* 53: 866–75 (June), 1959.

Hematologic (hematocrit, sedimentation time, red and white blood cells) and blood coagulation studies were carried out for man, rhesus monkey, cow, sheep, dog, cat, rabbit, raccoon, opossum, chicken and duck. Variations among species are discussed.

446. EITZMAN, D. V. AND SMITH, R. T. Antibody response to heterologous protein in rabbits of varying maturity. *Proc. Soc. Exptl. Biol. Med.* 102: 529–31 (Dec.), 1959.

On the basis of experiments in which New Zealand white rabbits were challenged by single injections of crystalline bovine albumin at ages of 2–30 days, evidence was obtained that a qualitative defect in immunological capacity exists in the neonatal rabbit. No immune response to the protein was obtained under 14 days of age; variable response was obtained at ages 14–28 days, and consistent production of antibodies was observed in rabbits older than 28 days.

447. EVERETT, N. B. AND YOFFEY, J. M. Life of guinea pig circulating erythrocyte and its relation to erythrocyte population of bone marrow. *Proc. Soc. Exptl. Biol. Med.* 101: 318–9 (June), 1959.

The life of circulating red cells in normal guinea pigs was determined autoradiographically, by injecting $Fe^{59}Cl_3$. For the first 7 days there was a linear increase in percentage of labeled erythrocytes. On the assumption that this represents the normal rate of new red cell formation, the life of the circulating red cell was calculated as 83 days. (Author's summary modified)

448. FLEISCHNER, J. R. AND SARGENT, F., II. Effects of heat and cold on the albino rat: crossed resistance or crossed sensitization? *J. Appl. Physiol.* 14: 789–97 (Sept.), 1959.

Two experiments were carried out to test whether or not cold-acclimatized rats adjust better to heat and heat-acclimatized rats adjust better to cold than rats not previously exposed to either environmental extreme. In both, groups of rats were exposed to 94.5°–96.5°F (hot), 33°–40°F (cold) and 76°–78°F (control). In the 1st experiment 45 female Holtzman littermates were used. After 50 days, "hot" rats were abruptly transferred to cold, "cold" rats to heat. Control animals were also placed in each environment. In the 2nd experiment 55 identical rats were similarly treated; the cross, however, was made after 29 days. Rats exposed to 95°F exhibited sustained hypothermia. Rats exposed to 36°F developed a transient hypothermia which lasted longer in the 1st experiment than in the 2nd and was accompanied by more severe cold injury. Heat was not a stress in the sense of Selye, but cold was. There was crossed sensitization rather than crossed resistance. (Author's summary)

449. FRANKEL, H. M. Effects of restraint on rats exposed to high temperature. *J. Appl. Physiol.* 14: 997–9 (Nov.), 1959.

Male rats were placed in a cage either 8 in. x 8 in. x 10 in. (free) or 2 in. x 2 in. x 8 in. (restrained) and exposed to ambient temperatures between 40° and 60°C. "Restrained" rats died sooner than "free" animals at all temperatures. There was no significant difference between final rectal temperatures of free and restrained rats at ambient temperatures greater than 40°C; mean for these groups was 44.6°C. At 40°C the final rectal temperature was slightly lower in the restrained group (43.4° vs. 44.6°C). Restraint had no significant effect on the constituents of the blood examined. Serum potassium and specific gravity and blood hematocrits were increased and serum sodium was unchanged in heat-exposed rats compared with controls at 26°C. Serum calcium varied irregularly with exposure temperature. (Author's summary)

450. FRIEDMAN, J. J. Circulating and tissue hematocrits of normal unanesthetized mice. *Am. J. Physiol.* 196: 420–2 (Feb.), 1959.

The circulating and tissue hematocrits of normal unanesthetized mice were determined by means of independent red cell and plasma volume measurements. The red cell volume indicator was radioiron (Fe^{59})-tagged red cells. The hematocrits of the various tissues were: spleen 51.3%, lung 47.9%, muscle 49.9%, liver 38.9%, intestine 32.2%, skin 29.2% and kidney 24.0%. The total body hematocrit was 35.4% as compared to 48.4% for venous blood. All tissues, with the exception of spleen and lung, contained hematocrits which were lower than that of venous blood suggesting the presence of some mechanism within the various tissues which is capable of effectively separating plasma from red cells. (Author's summary)

451. GORCZYCA, L. R., MCCARTY, R. T. AND LIMON, J. M. Studies of goat serum proteins by paper electrophoresis. *Am. J. Vet. Research* 20: 921–4 (Sept.), 1959.

The normal concentration of albumin, globulin and globulin fractions as well as the number and mobilities of the various protein components were determined by electrophoresis. Total proteins were determined by a chemical method. The following mean values (gm/100 ml) and standard deviations were found: total protein 6.25 ± 0.35, albumin 3.95 ± 0.26, α-globulin 0.42 ± 0.09, β_1-globulin 0.83 ± 0.12, β_2-globulin 0.41 ± 0.07, γ-globulin 0.97 ± 0.18.

452. GORDON, H. A. Morphological and physiological characterization of germfree life. *Ann. N.Y. Acad. Sci.* 78, Art. 1: 208–20 (May), 1959.

The presently available germfree chickens, rats, and mice compare satisfactorily to their counterparts in the normal-stock colony in terms of development and general health. Germfree chickens and rats, in comparison to normal-stock controls, were found to display reduced weight, water, reticuloendothelial tissue and connective tissue content in such organs as are normally in contact with the flora. The same findings, although less extensively tested, were made also in germfree mice. It is assumed that these characteristics of the germfree animal are caused primarily by the lack of the stimulation that would be caused by flora. The enlarged cecum of the germfree rodents appears to have a more complex etiological background. The slight retardation of growth and adrenal enlargement that was observed in these animals has tentatively been

brought into association with this unusual mass in the abdominal cavity. (Author's summary)

453. GREENE, E. C. *Anatomy of the Rat.* (*Trans. Am. Phil. Soc. New Series* Vol. 27) New York, Hafner Pub. Co., 1959, 370 pp.

The book contains chapters on: General appearance, skeleton, muscles, viscera, endocrines, nervous and circulatory system. A bibliography is included.

454. GRIFFITH, D. R. AND TURNER, C. W. Normal growth of rat mammary glands during pregnancy and lactation. *Proc. Soc. Exptl. Biol. Med.* 102: 619–21 (Dec.), 1959.

The use of desoxyribonucleic acid as a quantitative index of mammary gland cellular proliferation in rats is reported. A 41.5% increase of the mammary gland was found in Sprague-Dawley-Rolfsmeyer rats between the 18th and 20th day of pregnancy and the 5th day of lactation. The glandular proliferation was not interfered with by ovariectomy.

455. HAFEZ, E. S. E. Reproductive capacity of farm animals in relation to climate and nutrition. *J. Am. Vet. Med. Assoc.* 135: 606–14 (Dec. 15), 1959.

The effects of thermal, daylight, nutritional and exteroceptive environment on fertility and related phenomena is reviewed. (95 references)

456. HALE, H. B., MEFFERD, R. B., JR., VAWTER, G., FOERSTER, G. E. AND CRISCUOLO, D. Influence of long-term exposure to adverse environments on organ weights and histology. *Am. J. Physiol.* 196: 520–4 (Mar.), 1959.

Male Sprague-Dawley rats, caged individually, were exposed to cold (3° or 5°C), neutral (24°–6°C), hot (34°–5°C) or altitude (simulated with temperature at the neutral level). Organ weights (liver, heart, kidney, spleen, thymus, adrenal and testes) were determined after 24 wk. of exposure. Histological preparations of all of these organs as well as pituitary, thyroid, parathyroid, parotid, submaxillary glands, pancreas, tongue and brain were studied.

457. HAMMOND, J., ed. *Progress in the Physiology of Farm Animals. Supplement.* London, Butterworth & Co., 1959, pp. 1047–1116.

The section on reproduction in animals is continued.

458. HANNON, J. P. AND YOUNG, D. W. Effect of prolonged cold exposure on the gross blood composition of the rat. *Am. J. Physiol.* 197: 1008–12 (Nov.), 1959.

Adult male Sprague-Dawley rats, weighing 275–325 gm, were exposed to temperatures of 5° ± 1°C for 28–32 days. Hematocrit, hemoglobin, plasma water, plasma specific gravity, plasma protein and nonprotein N, blood glucose, total plasma lipids, plasma phospholipids, plasma cholesterol and blood ketones were determined in nonfasted and fasted condition for the cold-exposed rats and controls kept at 25 ± 1°C.

459. HARE, W. C. D. Radiographic anatomy of the feline skull. *J. Am. Vet. Med. Assoc.* 134: 349–56 (Apr. 15), 1959.

The anatomy of the feline skull is described.

460. HARRINGTON, J. D. AND NARDONE, R. M. Hepatic function of the golden hamster after exposure to cold and during hibernation. *Am. J. Physiol.* 196: 910–12 (Apr.), 1959.

The effect of forced hypothermia, long-term cold exposure and hibernation on liver function of the golden hamster, *Mesocricetus auratus*, was studied in order to ascertain the role of the liver in survival of a hibernator under cold stress. The Bromsulphalein test for liver function indicated no liver damage from forced hypothermia and 3.5% liver impairment from long-term cold exposure. The colloidal red flocculation test for liver function showed an upset of serum albumin/globulin ratio after long cold exposure and during hibernation. This is correlated with prolongation of blood clotting time observed during hibernation. These factors are used to exemplify the importance of the liver in hibernal physiology.

461. HEREMANS, J., CLAUSEN, J., HEREMANS, M. T. AND RASK-NIELSEN, R. Immunoelectrophoretic characteristics of normal mouse serums as a basis for studying pathological changes in serums of mice carrying transplantable malignant growths. *J. Natl. Cancer Inst.* 22: 45–56 (Jan.), 1959.

An immunoelectrophoretic method for the study of serum from normal (CBA × DBA/2)F_1 hybrid mice with special reference to the β- and γ-regions, is described. More than 20 specific precipitation lines can be distinguished in the whole-serum electrophoresis, 9 of which belong to the β- and γ-regions. Some characteristic features are mentioned for each of these lines. (Condensed from author's summary)

462. HURLEY, L. S. AND EVERSON, G. J. Delayed development of righting reflexes in offspring of manganese-deficient rats. *Proc. Soc. Exptl. Biol. Med.* 102: 360–2 (Nov.), 1959.

Development of righting reflexes was studied in offspring of Mn-deficient and normal rats by 2 tests: *1*) time required to turn from their backs to their feet and *2*) ability to right themselves in air when dropped upside down. The reflexes concerned with the turnover test developed at an earlier age than did those involved in the air-righting response. In both tests, however, the Mn-deficient young exhibited a marked delay in development of reflexes responsible for righting reactions. (Author's summary)

463. HURLEY, L. S., EVERSON, G. J. AND GEIGER, J. F. Serum alkaline phosphatase activity in normal and manganese-deficient developing rats. *J. Nutrition* 67: 445–50 (Mar. 10), 1959.

Serum alkaline phosphatase activity was determined in the young of normal and Mn-deficient female rats maintained on fortified fresh milk diets, from the 18th day of gestation to 28 days after birth. Mn deficiency had no significant effect upon the serum phosphatase at any of the ages examined. Both Mn-supplemented and Mn-deficient young exhibited a rise in alkaline phosphatase activity from the 18th day of gestation to birth followed by a plateau to 18 days, when a sharp rise began which continued to 28 days of age. (Author's summary)

464. HUTH, E. J. AND ELKINTON, J. R. Effect of acute fasting in the rat on water and electrolyte content of serum and muscle and on total body composition. *Am. J. Physiol.* 196: 299–302 (Feb.), 1959.

Thirteen acutely fasted male adult rats were compared with 6 fed controls in respect to serum electrolyte levels (7 rats), total carcass (7 rats) and skeletal muscle composition (13 rats). Of the serum electrolyte levels only K was mildly depressed. The loss of weight ranged between 25% and 37% of the initial value (mean = 32%). Total body fat was decreased most (mean = −97%). Lean body mass was relatively increased from 90% to 99% of the final body weight, but was absolutely decreased by 25% of the initial value; the ratio of water to fat-free solids was unchanged. In the total fat-free carcass, chloride was increased more than Na; K was decreased relative to the total wet tissue, to total water and to N. (From author's summary)

465. Isojima, S., Graham, R. M. and Graham, J. B. Sterility in female guinea pigs induced by injection with testis. *Science* 129: 44 (Jan. 2), 1959.

Adult virgin female guinea pigs were injected with an emulsion of homologous adult testis and Freund's adjuvant before exposure to males. The fertility of this group was only 24% while the fertility of the control group was 84%. The testis-injected guinea pigs had also a high titer of antibodies against testis. (Author's summary)

466. Johnson, R. M. and Albert, S. Biochemical changes occurring in mouse liver cells with ageing. *Proc. Soc. Exptl. Biol. Med.* 102: 373–4 (Nov.), 1959.

The N and P contents of large and small granules and cytoplasmic supernatant were measured in liver cells from inbred virgin female mice of the C3H/Sp strain, 1½–21 mo. of age. Changes in relative amounts of N and P were found in all 3 subcellular fractions as the animals aged.

467. Joysey, V. C. The relation between animal and human blood groups. *Brit. Med. Bull.* 15: 158–64 (May), 1959.

Antigens of red and white blood cells and platelets, serum antigens and hemoglobins are discussed in this review. Blood group patterns are given for rabbits, cats, dogs, horses, pigs, cattle, sheep and chickens. Many references are listed.

468. Just, T. The ecological approach to germfree life studies. *Ann. N. Y. Acad. Sci.* 78, Art. 1: 371–4 (May), 1959.

The present status and future development of germfree life studies are briefly discussed. The term "biontology" is proposed for the entire field of research dealing with all germfree forms, and a system of biontological formulas, representing a code or system of shorthand characterizations giving all essential details relative to a particular experimental animal, such as origin, operation, food, and length of life in germfree environment, is recommended.

469. Kao, K.-Y. T. and McGavack, T. H. Connective tissue: I. Age and sex influence on protein composition of rat tissues. *Proc. Soc. Exptl. Biol. Med.* 101: 153–7 (May), 1959.

The content of soluble protein, soluble collagen, insoluble collagen and elastin was determined in tissues from tail tendon, aorta, skin, uterus, lung, muscle, heart, liver, kidney and spleen of male and female Wistar rats at 3–5 wk., 8 mo. and 2 yr. of age. The method of determination is described.

470. Kent, G. C., Jr. and Atkins, G. Duration of pseudopregnancy in normal and uterine-traumatized hamsters. *Proc. Soc. Exptl. Biol. Med.* 101: 106–7 (May), 1959.

An 8- to 10-day pseudopregnancy period occurs in most hamsters, the 9-day interval predominating. Hamsters rendered pseudopregnant by sterile mating do not exhibit a statistically significant prolongation of pseudopregnancy following uterine trauma, however massive, by interrupted sutures. The observations indicate species differences in luteal function in pseudopregnant hamsters as contrasted with rats. (Author's summary)

471. Kibrick, A. C., Safier, L. B. and Skupp, S. J. Existence of fatty acid peroxides in normal blood and tissues of man and animals. *Proc. Soc. Exptl. Biol. Med.* 101: 137–9 (May), 1959.

The presence of fatty acid peroxides in the tissues and blood of normal rats was demonstrated. A modified method in presence of 1.2×10^{-4} M ferric chloride has been developed for thiobarbituric acid reaction, which apparently yields values for fatty acid peroxides in blood as well as in tissues. (Condensed from author's summary)

472. Landry, S. O., Jr. Lactation hair in the Asiatic squirrel and relationship of lactation hair to mammary hair. *Science* 130: 37 (July 3), 1959.

A hair growth around the nipples during lactation is described in 2 species of the Asiatic squirrel genus *Callosciurus*. The term lactation hair is coined for this phenomenon, which is shown to be different from mammary hair in the sense for which that term was coined. (Author's summary)

473. Larsen, E. G. and Lacefield, D. J. Enzymatic synthesis of the porphyrins in the fox squirrel, *Sciurius ludovicianus*. *Federation Proc.* 18: Abstr. No. 1066 (Mar.), 1959.

Excessive enzymatic synthesis indicating a definite porphyria in *S. ludovicianus* was established by a quantitative determination of the following compounds in the urine; delta-amino levulinic acid (1.6 mg/day), porphobilinogen (0.8 mg/day) and total porphyrins (9.5 mg/100 ml urine). Chromatographic separation of the porphyrin methyl esters on paper and silica gel demonstrated the presence of the I and III isomers of copro- and uroporphyrins possessing 3, 5 and 7 carboxyl groups.

474. Lee, C.-C., Herrmann, R. G. and Froman, R. O. Serum, bile and liver total cholesterol of laboratory animals, toads and frogs. *Proc. Soc. Exptl. Biol. Med.* 102: 542–4 (Dec.), 1959.

Serum, bile and liver total cholesterol concentrations are tabulated for the rhesus monkey, mongrel dog and cat, albino rabbit, guinea pig, golden hamster, albino rat and mouse, pigeon, toad and frog.

475. Levenson, S. M., Crowley, L. V., Horowitz, R. E. and Malm, O. J. The metabolism of carbon-labeled urea in the germfree rat. *J. Biol. Chem.* 234: 2061–2 (Aug.), 1959.

Germfree rats of the white Lobund strain were used to test and confirm the assumption that enzymatic hydrolysis of urea in mammals is effected only by urease of the bacteria present in the gut. C^{14}-urea was used subcutaneously in germfree and normal control rats.

476. Lin, E. C. C., Rivlin, R. S. and Knox, W. E. Effect of body weight and sex on activity of enzymes involved in amino acid metabolism. *Am. J. Physiol.* 196: 303–6 (Feb.), 1959.

The total body activities of 4 transaminases and 2 oxidases concerned with aromatic amino acid metabolism were studied in RAP mice, golden hamsters, albino rats from an inbred strain of Slonaker rats, guinea pigs and New Zealand albino rabbits, to test for correlations between total body enzyme activity and body weight.

477. LINDSAY, H. A. AND DAWSON, R. L. Serum cholinesterase in normal and hypothyroid dogs. *Federation Proc.* 18: Abstr. No. 369 (Mar.), 1959.

Dogs were used to enable repeated samplings of blood; serum cholinesterase activity was measured spectrophotometrically with benzoylcholine as substrate. Esterase activity was determined in a control period in 2 groups of 5 animals and was found to be fairly constant. Oxygen use was determined under pentobarbital anesthesia. Rate of formation of enzyme was then determined in *group 1* by giving enough DFP to reduce the enzyme activity to essentially zero and noting the rate of return of activity. Rate of destruction was measured in *group 2* by injecting concentrated esterase intravenously and noting the time required for the activity to fall back to normal.

478. LINDSEY, A. W. AND GUYTON, A. C. Continuous recording of pulmonary blood volume: pulmonary pressure and volume changes. *Am. J. Physiol.* 197: 959–62 (Nov.), 1959.

A method for continuous recording of pulmonary blood volume in the intact animal has been devised, utilizing the detection of I^{131}-tagged blood from a circumscribed portion of lung field. The method was applied to 50 adult mongrel dogs anesthetized with sodium pentobarbital (30 mg/kg) and heparinized with 5 mg/kg of heparin. Graphs show the typical changes in pulmonary blood volume, systemic and pulmonary arterial pressure and left arterial pressure as the ascending aorta or pulmonary artery was progressively constricted.

479. MCARTHUR, W., OGAWA, T. AND NECHELES, H. Gastric distensibility and age in the mouse. *Am. J. Physiol.* 196: 979–80 (May), 1959.

Albino Swiss male mice of the Rockland RAP strain were killed and after several manipulations a small plastic tube was tied into the esophagus. Saline solution was injected slowly until a gastric perforation occurred. Gastric perforations were produced with considerably less pressure and smaller volumes of saline in young mice than in older ones. A possible relationship between intragastric pressure, circulation and ulceration is discussed.

480. MARSHALL, R. J., SEMLER, H. J. AND SHEPHERD, J. T. Blood volume components in the dog. *Federation Proc.* 18: Abstr. No. 389 (Mar.), 1959.

Indicator dilution curves were obtained in 7 anesthetized dogs by use of multiple injection (femoral vein, superior vena cava, pulmonary artery) and sampling (pulmonary artery, aortic valve, femoral artery) sites. The average lung and left-heart volume was 146 ml/10 kg, of which about 100 ml was contained in the lungs. Venous, arterial and right-heart volumes were respectively 97, 86 and 44 ml/10 kg. By analysis of suitable curves a figure for effective circulating blood volume was also derived, averaging 680 ml/10 kg (about 85% of predicted total blood volume).

481. MASON, M. M. *Bibliography of the Dog.* Ames, Iowa State Univ. Press, 1959, 401 pp.

The aim of this bibliography of 12,369 references has been to collect all the recent literature concerning the dog in the categories of natural and experimental data: natural diseases; techniques in surgery and physiology; anatomy; nutrition; biochemistry; genetics; pathology; immunology and virology; pharmacology; parasitology; hematology. The references are arranged alphabetically by author; a detailed subject index is included.

482. MIYAKAWA, M. The lymphatic system of germfree guinea pigs. *Ann. N. Y. Acad. Sci.* 78, Art. 1: 221–36 (May), 1959.

Germfree guinea pigs of the Gifu uniform strain were reared on a specified fluid diet for the 1st month and thereafter on a solid diet; the composition of both diets is listed. The lymphatic tissue was examined in conventional, germfree and monocontaminated animals. The germfree guinea pigs showed less developed lymphatic tissue than the conventional controls and no typical clear-centered nodules. However, these nodules could most easily be produced by monocontamination with a mildly toxic species of *Coccus*.

483. MOINUDDIN, J. F. AND LEE, H. W. T. Possible associations of dietary residues with growth of the large gut. *Am. J. Physiol.* 197: 903–11 (Oct.), 1959.

Diets containing 67% cornstarch, or 42% cornstarch plus 25% lactose, agar, cellulose or raw potato starch, were fed to rats. Dimensions of the cecum and colon plus rectum and many characteristics of large intestinal and fecal residues were recorded. (From author's summary)

484. NADEL, E. M., YOUNG, B. G. AND HILGAR, A. G. Strain differences in urinary hydroxycorticosteroids in guinea pigs. *Am. J. Physiol.* 196: 273–5 (Feb.), 1959.

A study of the daily excretion of 3 unconjugated, polar corticosteroids (6β hydroxycortisol, 2α hydroxycortisol and cortisol) was undertaken over a 24-day period in noninbred (Hartley albino) as well as inbred (strain 2 and strain 13) guinea pigs, prior to and immediately following the administration of 10 units of ACTH using established methods. (Condensed from author's summary)

485. NATHAN, D. G. AND WARREN, K. S. A colorimetric method for the measurement of the brain ammonia of the mouse: The effect of glutamine on the total measurable ammonia. *Arch. Biochem. Biophys.* 81: 377–81 (Apr.), 1959.

A method for brain ammonia analysis has been described. The mean concentration of ammonia nitrogen was found to be 0.46 ± 0.035 mg (32.2 ± 2.45 μM) per 100 gm of mouse brain. The contribution of glutamine hydrolysis by alkali to the brain ammonia concentration was significant, but was relatively constant. (Author's summary)

486. NATIONAL RESEARCH COUNCIL, COMMITTEE ON THE HANDBOOK OF BIOLOGICAL DATA. *Handbook of Circulation*, edited by D. S. DITTMER AND R. M. GREBE. Philadelphia, Saunders, 393 pp.

Data applying to man, other animals, including all common laboratory animals, and plants are arranged in tables, graphs, diagrams and drawings, and organized into the following categories: circulatory anatomy, chemical composition and physical properties, blood volumes, cardiac output, heart rate, blood pressures, blood and lymph flow, EKG, heart sounds and murmurs, effect of pregnancy, of compression, decompression and acceleration, and of radiation, blood coagulants and anticoagulants, effect of drugs and chemical substances, effect of pathological conditions.

XUM

487. NEELY, W. A. Apparent sodium space of the dog. *Am. J. Physiol.* 196: 1333–5 (June), 1959.

The sodium space should be equal to the space occupied by the total body water (TBW) (obtained by dividing the amount of sodium chloride injected by the change of concentration of the substance in question). The actual sodium space is larger than TBW; it must be a nonwater space (possibly bone).

488. PAREIRA, M. D., SERKES, K. D. AND LANG, S. Influence of mixing time on determination of red cell volume in normal and shocked rats. *Proc. Soc. Exptl. Biol. Med.* 101: 233–5 (June), 1959.

Determinations of red cell volume using Cr^{51}-tagged red cells have been made in normal and tourniquet-shocked rats using varied mixing times. Red cell volume determinations were significantly reproducible in the normal rat using mixing times of from 5 to 30 min. A 15-min. mixing time in the tourniquet-shocked rats allowed significantly reproducible determinations of the red cell volume. (Author's summary)

489. PAULY, J. E. The comparative anatomy of the adrenals. *Proc. Animal Care Panel* 9: 143–54 (Dec.), 1959.

A description is given of the adrenal cortices of the horse, lamb, goat, pig, calf, rabbit, dog, cat, guinea pig, rat, and man. Two theories on the mode of growth and cellular replacement are discussed.

490. PEACOCK, L. J. AND ROGERS, C. M. Gestation period and twinning in chimpanzees. *Science* 129: 959 (Apr. 10), 1959.

The length of the gestation period in 118 births in a colony of chimpanzees was found to be 226.8 days, with a standard deviation of 13.3 and a range of 196–260 days. Six pairs of twins were born in 120 parturitions; thus the apparent twinning rate is higher than in man. (Author's abstract)

491. PERK, K. AND LOBL, K. Serum cholesterol and paper electrophoretic lipoprotein pattern in cattle. *Am. J. Vet. Research* 20: 989–91 (Nov.), 1959.

Total cholesterol levels and paper electrophoretic lipoprotein patterns were analyzed in the serums of normal cattle of both sexes belonging to different age groups. Total cholesterol values and alpha lipoprotein values for heifers exceeded those of bull calves; castrated bull calves showed intermediate values. The corresponding total serum cholesterol and alpha lipoprotein values of pregnant and lactating cows were significantly higher than those of bull calves, castrated bull calves, and heifers. (Author's summary)

492. POMERANZE, J., PILIERO, S. J., MEDECI, P. T. AND PLACHTA, A. Deficiency diets in young growing rats. *Proc. Soc. Exptl. Biol. Med.* 100: 207–10 (Jan.), 1959.

The weights of pituitary, adrenal, spl :n, thymus and testes of young rats of closely inbred modified Long-Evans strain on a normal diet or on diets deficient in amino acids are reported. Gross and histologic changes on deficient diets were demonstrated.

493. RADFORD, E. P., JR. Factors modifying water metabolism in rats fed dry diets. *Am. J. Physiol.* 196: 1098–108 (May), 1959.

The influence of addition of large amounts of NaCl or urea, a protein-free diet with or without urea added, and diets containing various levels of Na, K and Cl upon the water turnover in rats was studied.

494. ROSENTHAL, H. L. Absorption, excretion and tissue distribution of oral cyanocobalamin in rabbits. *Am. J. Physiol.* 197: 1048–52 (Nov.), 1959.

Author points out that in rabbits the ingestion of vitamin B_{12} from coprophagy of feces may explain its relatively large urinary excretion. Fecal vitamin B_{12} is formed in large quantity in rabbits consuming diets practically devoid of the vitamin. The mechanism of gastrointestinal absorption of vitamin B_{12} in rabbits was studied by radioactive tracer methods. Vitamin B_{12} absorption in rabbits was found to be similar to that in other laboratory animals and man.

495. SALZANO, J. AND HALL, F. G. Influence of vagal blockade on respiratory work in the hypoxic and hypercapneic anesthetized dog. *J. Appl. Physiol.* 14: 348–52 (May), 1959.

The mechanical work of breathing was determined in anesthetized dogs by measurements of intrathoracic pressures and tidal volumes, during inhalation of various gas mixtures while vagi reflexes were functional (warm), and blocked (cool). Average values of observations made during inhalation of room air and CO_2 or low O_2 gas mixtures before and during vagal cooling are tabulated. The data show that none of the observed changes in the respiratory work components can be correlated with the cardiovascular alterations produced by vagal cooling.

496. SAPIRSTEIN, L. A. AND HARTMAN, F. A. Cardiac output and its distribution in the chicken. *J. Am. Physiol.* 196: 751–2 (Apr.), 1959.

The cardiac output of the chicken has been measured by the indicator dilution technique and its distribution determined by the indicator distribution technique. The cardiac output is 218 ml/kg/min. The coronary flow fraction is 4.9% of the cardiac output, the renal flow fraction, 15.2% of the cardiac output, and the splanchnic flow fraction, 17.4% of the cardiac output. The perfusion rates of the thyroid and adrenal glands are similar to those found in the rat. (Author's summary)

497. SCHNEYER, C. A. AND SCHNEYER, L. H. Electrolyte levels of rat salivary secretions. *Proc. Soc. Exptl. Biol. Med.* 101: 568–9 (July), 1959.

Submaxillary-sublingual and parotid gland secretions were collected directly from salivary glands of fasted, lightly anesthetized adult male Long-Evans rats for an initial period of 3 min. during stimulation by subcutaneously injected pilocarpine. Determination of the electrolyte levels (Na, K, Na + K) revealed a broad correlation between gland Na and K levels.

498. SELLAR, R. F. AND SMART, J. V. Relationship between environment and response of mice in the biological assay of insulin. *J. Animal Technicians Assoc.* 9: 70–4 (Mar.), 1959.

Changes in temperature, in mice stored in a stock box or in illumination, before and during the test were found to affect the sensitivity of albino mice of the Swiss Schofield strain. Therefore, 2 batches of mice should not be pooled for assaying unless they have been kept under identical conditions since small changes in environment may produce very marked effects on their response.

499. SPRINGER, G. F., HORTON, R. E. AND FORBES, M. Origin of antihuman blood group B agglutinins in germfree chicks. *Ann. N. Y. Acad. Sci.* 78, Art. 1: 272–5 (May), 1959.

Antihuman blood group B agglutinins in chicks are not inherited but acquired early in life.

500. STRAUB, O. C., SCHALM, O. W., HUGHES, J. P. AND THEILEN, G. H. Bovine hematology. II. Effect of parturition and retention of fetal membranes on blood morphology. *J. Am. Vet. Med. Assoc.* 135: 618–22 (Dec. 15), 1959.

Total leukocyte counts in cows after parturition were significantly elevated. By the 1st day post partum the total count fell sharply. When the fetal membranes were retained, all leukocyte types were depressed below the levels on the 2nd post-partum day.

501. TEODORU, C. V. AND GRISHMAN, E. Alterations of the interscapular brown fat (hibernating gland) during pregnancy in hamsters. *Federation Proc.* 18: Abstr. No. 2012 (Mar.), 1959.

Adrenals, thymus and interscapular brown fat were examined in 60 pregnant and 60 virgin female hamsters of the same age and breed. Adrenals were significantly enlarged during pregnancy (25 mg/100 gm vs. 14 in control). Fasciculata cells were hypertrophic, granular and lighter stained. Alkaline phosphatase activity was markedly increased in the cortex of pregnant as compared to control hamsters. The thymus diminished significantly in pregnant hamsters (41 mg/100 gm vs. 63 in control).

502. TEODORU, C. V., SAIFER, A. AND FRANKEL, H. Conditioning factors influencing evolution of experimental glomerulonephritis in rabbits. *Am. J. Physiol.* 196: 457–60 (Feb.), 1959.

Included in the study were control values for the following: various constituents of serum, daily volume and specific gravity of urine, albumin in urine and total albumin loss.

503. THORBECKE, G. J. Some histological and functional aspects of lymphoid tissue in germfree animals. I. Morphological studies. *Ann. N. Y. Acad. Sci.* 78, Art. 1: 237–46 (May), 1959.

The organs studied were spleen, thymus, bursa of Fabricius and lymphoid tissue of the intestinal tract in the chicken and spleen, mesenteric lymph nodes and lymphatic tissue of the intestinal tract in rats. Frequencies of occurrence of plasma cells and secondary nodules in germfree, control and monocontaminated animals are tabulated.

504. THORBECKE, G. J. AND BENACERRAF, B. Some histological and functional aspects of lymphoid tissue in germfree animals. II. Studies on phagocytosis *in vivo*. *Ann. N. Y. Acad. Sci.* 78, Art. 1: 247–53 (May), 1959.

The rates of clearance for C particles and for heat-killed, P^{32}-labeled bacteria from the blood stream were studied in germfree and control mice. No significant difference in C clearance was noted in the 2 groups. Clearance of *E. coli* was slower in germfree mice while that of *Staph. aureus* was similar in germfree and control mice. The general conclusion drawn is that germfree animals usually show a lower development of lymphoid tissue, lower serum gamma-globulin levels and in some cases lower phagocytic indices for bacteria.

505. TRAPANI, I. L. AND CAMPBELL, D. H. Passive antibody decay in rabbits under cold or altitude stress. *J. Appl. Physiol.* 14: 424–6 (May), 1959.

Rabbits maintained at an environmental temperature of −15°C (5°F) for 10 wk. exhibit an increase in the decay rate of passively administered antibody. Rabbits acclimatized at an altitude of 12,470 ft. for 30 days show little or no change in passive antibody decay. Protein turnover in these groups of animals is discussed. (Author's summary)

506. VESSELINOVITCH, S. D. The analysis of serum proteins of domestic animals by filter-paper electrophoresis. A review. *Cornell Vet.* 49: 82–96 (Jan.), 1959.

The analysis of serum proteins by filter-paper electrophoresis is described and relative percentages of serum-protein fractions (albumin α-, β- and γ-globulin) of horse, cow, swine, sheep, goat and dog and newborn and young pigs are reported.

507. WAGNER, M. Determination of germfree status. *Ann. N. Y. Acad. Sci.* 78, Art. 1: 89–100 (May), 1959.

The determination of germfree status requires microscopic and/or culture methods. A general scheme for determining the germfree status of an animal is presented. The term germfree is measured in terms of failure to demonstrate viable forms exclusive of the animal under test and can be applied only when accepted procedures have failed to produce evidence of contamination. Methods used for the determination of the germfree status of animal colonies are discussed.

508. WAGNER, M. Serologic aspects of germfree life. *Ann. N. Y. Acad. Sci.* 78, Art. 1: 261–71 (May), 1959.

The occurrence of heterohemagglutinins and antibacterial agglutinins was determined in the sera of germfree and conventional chicken and rats. Limited observations were made on properdin and complement titers in germfree rats.

509. WEGELIUS, O. The dwarf mouse—an animal with secondary myxedema. *Proc. Soc. Exptl. Biol. Med.* 101: 225–7 (June), 1959.

The level of protein-bound iodine in serum of dwarf mice was found to be very low in comparison to the value obtained on serum of normal siblings. Thyroids of untreated dwarf mice did not accumulate I^{131} whereas injection of thyrotropin stimulated the glands to I uptake. It was concluded that the dwarf mouse is a secondary myxedematous animal because of deficient production or complete lack of thyrotropic pituitary hormone. (Author's summary modified)

510. WEIMER, H. E., BELL, R. T. AND NISHIHARA, H. Dietary protein and serum electrophoretic patterns of the adult rat. *Proc. Soc. Exptl. Biol. Med.* 100: 853–5 (Apr.), 1959.

Electrophoretic analyses of the serum proteins of normal adult male Sprague-Dawley rats and the hemoglobin and hematocrit values are included in investigations of the effects of inanition, acute and chronic protein depletion and of repletion with several levels of proteins. The lability of serum proteins of the adult rat to dietary influences suggests the use of this species in nutrition studies.

511. WHITTEN, H. Biologically important animals of Louisiana: the armadillo. *Carolina Tips* 22: 19 (June), 1959.

The armadillo, which at every birth produces quadruplets by fission of the fertilized egg, is suitable for certain genetic experiments. The quads are either all males or all females.

512. WILDFÜHR, G., NAUMANN, G. AND WILDE, J. Das normale Elektropherogramm des Rattenserums und

seine Veränderung durch Antigenapplikation. (Normal electrophoretogram of rat blood and its change by means of antigen administration.) *Acta Biol. Med. Germanica* 2, No. 1: 24–38, 1959.

The protein fractions in the serum were determined electrophoretically in 105 normal rats, 150–200 gm weight, 7–12 mo. old. The paper electrophoretic strips were evaluated by the elution or by the transparency method. The distribution of the fractions was found to vary with the age of the animals. Another group of rats was injected with toxoplasmas and electrophoretograms were taken 16–17 days and 45–55 days after the infection. The results are discussed.

513. WOLFE, H. G. Blood-pH differences in two inbred strains of mice. *J. Heredity* 50: 155–8 (July–Aug.), 1959.

Blood-pH determinations were made in 2 strains of mice (a high blood pH and a low blood pH), using a research type Cambridge pH meter. Samples were obtained by cardiac puncture. The mean pH in arterial and venous blood was 7.480 ± 0.0062 and 7.428 ± 0.0065 for the high blood-pH strain, and 7.475 ± 0.0076 and 7.381 ± 0.0084 for the low blood-pH strain. No effect of age on pH was noted.

514. WOSTMANN, B. S. Serum proteins in germfree vertebrates. *Ann. N. Y. Acad. Sci.* 78, Art. 1: 254–60 (May), 1959.

Electrophoretic patterns of the serum of normal and germfree chickens, rats, mice, guinea pigs and rabbits are shown. A certain content of gamma globulins was present in the serum of germfree rats, mice and chickens and probably in the rabbits; a definite lack of certain gamma fractions was noted in the germfree guinea pig. The latter finding might have been due to the fact that the guinea pigs were 1st-generation animals while the rats and mice were at least of the 5th generation. The serologic implication of these findings is discussed.

515. WOSTMANN, B. AND BRUCKNER-KARDOSS, E. Development of cecal distention in germ-free baby rats. *Am. J. Physiol.* 197: 1345–6 (Dec.), 1959.

The weight of the full cecum was determined in conventional and germfree Lobund strain female rats (of Wistar origin) at 7, 16, 25 and 42 days of age, using different diets. In the germfree rat cecal enlargement started during the 2nd wk. of life; at 25 days the full cecum was 5–7 times larger than in the conventional animal, a ratio which persisted from that time on. It is assumed that the cecal enlargement was not due to a nutritional deficiency but rather to the absence of certain stimuli normally arising from the presence of the microbial flora and/or its metabolic activity.

516. YOUNG, D. R. Effect of food deprivation on treadmill running in dogs. *J. Appl. Physiol.* 14: 1018–22 (Nov.), 1959.

Performance of dogs was measured by a plan of daily bouts of aerobic work on motor-driven treadmills at 3.63 mph and 10% of inclination in an air-conditioned laboratory (65°F and 50% relative humidity). Cardiorespiratory responses, water loss and body temperature for daily steady work were tabulated for controls and fasted dogs.

517. YOUNG, D. R., IACOVINO, A., ERVE, P., MOSHER, R. AND SPECTOR, H. Effect of time after feeding and carbohydrate or water supplement on work in dogs. *J. Appl. Physiol.* 14: 1013–7 (Nov.), 1959.

Male purebred beagle dogs, 17 mo. old, 8.4–12.1 kg weight, were maintained in a high state of physical conditioning for 7 mo. prior to being tested on motor-driven treadmills at 3.63 mph, at a controlled temperature of 65°F and 53% relative humidity. In the 1st series performance was tested after 1½, 4, 6 and 24 hr. following a meal; in a 2nd series effect of carbohydrate and water supplementation on maximum aerobic work capacity was determined 17 hr. after the last meal. In summary, a loss in economy of work at 4 and 6 hr. following a substantial meal was noted. Provision of water improved endurance capacity whereas sugar was without immediate benefit.

THE FOLLOWING ABSTRACTS, although located elsewhere in this bibliography, are related to the subject of this section.

Section 2: 9, 13, 18, 47, 70, 81, 83, 84, 90, 92, 98, 104, 114, 122, 126, 128, 135, 141, 143, 145, 155, 175, 178, 183, 192, 200, 201, 202, 214, 219, 225, 230, 232, 233, 239, 244, 269, 273, 298, 305, 330, 344, 355.

Section 3: 9, 10, 11, 12, 13, 21, 23, 32, 33, 34, 35, 36, 38, 39, 40, 42, 44, 46, 48, 50, 52, 56, 58, 60, 66, 67, 70, 72, 74, 75, 76, 78, 79, 82, 86, 87.

Section 4: 3, 9, 16, 17, 20, 22, 24, 30, 32, 34, 35, 37, 44, 46, 47, 49, 52, 53, 60, 61, 62, 67, 71, 73, 74, 84, 86, 88, 91, 94, 97, 105, 107, 110, 111, 112, 116.

Section 5: 19, 22, 34, 49, 90, 102, 108, 117.

Section 6: 4, 18, 23, 28, 29, 41.

Section 7: 12, 15, 19, 25, 45, 47, 49, 63, 67, 70, 73, 79, 86, 94, 95, 100, 102, 121, 138, 140, 156, 158, 164, 167, 169, 185, 191.

Section 9: 2.

2. Diseases, Abnormalities, Injuries[1]

Including Diagnostic Tests, Prevention, Eradication, Control, Treatment

1. SAUNDERS, C. G. *Rabbit and Cat Diseases.* Chicago, Am. Veterinary, 1919, 121 pp.

The following diseases of the rabbit are discussed: diseases of the digestive tract; coccidiosis; rabbit septicemia; infectious diseases (Schmorl's disease, streptobacillary pseudotuberculosis, urethritis, vaginitis, tuberculosis); skin diseases; diseases of pregnancy; miscellaneous diseases (anorexia, catarrh, hematuria, paraplegia, convulsions, wounds). For the cat: diseases of the digestive system; contagious diseases (feline distemper, feline diphtheria, tuberculosis); external parasites and skin diseases.

2. FOX, H. *Disease in Captive Wild Mammals and Birds.* Philadelphia, Lippincott, 1923, 665 pp.

Diseases of the following systems are discussed: heart; blood vessels; blood and bone marrow; lymphatic tissues including spleen; respiratory, alimentary and urinary tracts; reproductive organs; ductless glands; skeleton and joints; central nervous system and special senses; also discussed: constitutional and infectious diseases; neoplasms.

3. KEIL, H. L. AND NELSON, V. E. The role of copper in hemoglobin regeneration and in reproduction. *J. Biol. Chem.* 93: 49–57, 1931.

Nutritional anemia produced by a whole-milk diet causes a change in color of the coat of the rat, particularly in the dark-coated ones. Black or black-hooded rats change to a striking silvery gray while gray-coated animals change to a buff or silvery gray with a yellowish tint. These changes which are due to lack of Fe are noticeable in about 8 wk. Color is restored by addition of Cu and Fe to the whole milk, but not by addition of Fe alone.

4. SCHWARTZ, B. Rabbit parasites and their control. In: SCHWARTZ, B. AND SHOOK, W. B. *Rabbit Parasites and Diseases. U. S. Dept. Agr. Farmers' Bull.* No. 1568, Dec., 1928, rev. Feb., 1935, pp. 2–24.

External parasites and parasitic skin diseases, i.e. mange, wry neck, lice, fleas, chiggers and warbles, and internal parasites, i.e. protozoa (coccidia, intestinal flagellates) and worms (tapeworms, flukes, roundworms), as well as sanitary measures to control them, are discussed.

5. SHOOK, W. B. Bacterial and other diseases. In: SCHWARTZ, B. AND SHOOK, W. B. *Rabbit Parasites and Diseases. U. S. Dept. Agr. Farmers' Bull.* No. 1568, Dec., 1928, rev. Feb., 1935, pp. 25–30.

Hemorrhagic septicemia, contagious nasal catarrh, tularemia, necrobacillosis, pneumonia, indigestion, scours, constipation and sore backs in rabbits are discussed.

[1] Arrangement is chronological by year of publication. A list of additional references, located in other sections of this bibliography, will be found on page 78.

6. REBRASSIER, R. E. *Diagnosis of Parasites in Animals.* Columbus, Ohio State Univ. Press, 1938, 65 pp.

The techniques for the examination of feces and skin scrapings, and for testing for microfilaria in blood are concisely described. The major portion of the pamphlet is devoted to diagrams of the life cycle, and macro- and microphotographs of parasites of the horse, ruminant, swine, dog, cat and poultry.

7. SCHROEDER, C. R. A diagnostic test for the recognition of tuberculosis in primates; a preliminary report. *Zoologica* 23, Pt. 4: 397–400 (Dec. 31), 1938.

A 1% solution of purified protein derivatives tuberculin was injected into the margin of the upper eyelid of the restrained animal. A reaction in a tuberculous monkey will usually begin after 16 hr. and persist for 72 hr. depending upon the severity of the reaction. Primates too large for manual restraint are anesthetized. Animals should be retested after 2 mo. to detect infections which were not sufficiently advanced at the 1st test to produce a reaction.

8. VENARD, C. E. Morphology, bionomics, and taxonomy of the cestode, *Dipylidium caninum. Ann. N. Y. Acad. Sci.* 37, Art. 5: 273–328 (July 5), 1938.

The literature on the larval and adult stages of the dog and cat tapeworm, *Dipylidium caninum*, is reviewed. A method is described by which the life cycle was completed under experimental conditions. Observations on the morphology and bionomics of the larval and adult stages are given. (Condensed from author's summary)

9. HERMAN, C. M. *The Rabbit as Used in Disease Research. A Selected Bibliography Including the Spontaneous Diseases of Rabbits.* Chicago, Fish and Wildlife Service, U. S. Dept. of the Interior, 1942, 519 pp.

A bibliography of 4859 references on bacterial disease; virus disease and tumors; spirochetal disease; parasites, rickettsias, fungi; immunity and anaphylaxis; general physiology, anatomy and pathology; circulation; nutrition; endocrines; physiology of reproduction; pharmacology; general and miscellaneous.

10. CHEN, K. K., ANDERSON, R. C., STELDT, F. A. AND MILLS, C. A. Environmental temperature and drug action in mice. *J. Pharmacol.* 79: 127–32 (Oct.), 1943.

The toxicity of intravenously injected sulfapyridine, sulfathiazole, strychnine, picrotoxin, tutin, aconitine and scopolamine increases slightly as the ambient temperature increases. Diaminodiphenyl sulfone given orally is about 10 times as toxic at 40° as at 25C°. Intravenously administered insulin is more than 80 times as toxic at 40° as at 20° and harmine-HCl is twice as toxic at 40° as at 20°.

11. GRAHAM, R., LEVINE, N. D. AND MORRILL, C. C. Listerellosis in domestic animals. A technical discussion of field and laboratory investigations. *Univ. Illinois Agr. Expt. Sta. Bull.* 499 (Dec.), 1943, 99 pp.

The manifestations of *Listerella* infection in rabbits, guinea pigs, chickens, cattle, sheep, swine and horses are discussed.

12. LESTER, D. Formation of methemoglobin. I. Species differences with acetanilide and acetophenetidine. *J. Pharmacol. Exptl. Therap.* 77: 154–9 (Feb.), 1943.

The maximum amounts of methemoglobin produced by single doses of acetanilide and acetophenetidine in man, cats, dogs, rats, monkeys and rabbits were determined. The determinations were preliminary to a study of possible species differences in the intermediary metabolism of aniline derivatives. It was found that the rabbit and the monkey form virtually no methemoglobin with the drugs. In order of sensitivity to methemoglobin formation by these drugs, man is about ½ as sensitive as the cat, the dog ½ as sensitive as man and the rat ⅙ as sensitive as the dog. (28 references)

13. MILLS, C. A., COTTINGHAM, E. AND MILLS, M. Environmental temperature and vitamin K deficiency. *Am. J. Physiol.* 141: 359–62 (May), 1944.

Severe and highly fatal vitamin K deficiency was produced in rats adapted to tropical heat by feeding them K-free synthetic diets containing 0.5% sulfaguanidine. The blood clotting times after 9, 16, 23 and 30 days on this diet were recorded for rats kept at 68°F and at 90°–91° and 60%–70% humidity. The hemorrhagic crisis occurred early in the 3rd wk. and disappeared almost entirely by the 5th wk. The manifestations of K deficiency were much more severe in tropical heat than in temperate coolness.

14. RUCH, T. C. *Bibliography of Primate Malaria.* New Haven, Yale Medical Library, 1944, 59 pp.

A classified bibliography comprising 283 references is presented. Each abstract indicates the species of *Plasmodium*, the primate hosts, the vectors involved, and whether the study was experimental, purely morphological or a report of spontaneous occurrence.

15. UNGAR, G. The effect of trauma on bleeding time and capillary resistance. *J. Physiol. (London)* 103: 18–9P (July), 1944.

Traumatized guinea pigs showed a shortening of the bleeding time and an increase of capillary resistance. Blood serum of traumatized guinea pigs, when injected into normal animals, also shortens bleeding time and increases capillary resistance. It is assumed that these effects depend on some common factor acting on the capillary wall.

16. MOULTON, F. R., ed. *A Symposium on Mammary Tumors in Mice.* Washington, D.C., Am. Assoc. for the Advancement of Science (*Publication* No. 22), 1945, 223 pp.

The following aspects are discussed: Cytology of mammary tumors of the mouse; morphology and histogenesis of mammary tumors; histogenesis of the mammary gland of the mouse; the vascular supply of mammary gland carcinomas; genetics of mammary tumors in mice; hormones and mammary cancer in mice; the milk influence in the genesis of mammary tumors; diet and some other environmental influences in the genesis and growth of mammary tumors in mice; the chemistry of the mammary tumors; experimental treatment of mammary tumors in mice; conclusions, including discussion of the possible implications for man.

17. RATCLIFFE, H. L. Infectious diseases of laboratory animals. *Ann. N. Y. Acad. Sci.* 46, Art. 1: 77–96 (June 15), 1945.

The following infectious diseases of laboratory animals are reviewed: Bacterial diseases, pneumonia, spirochetal infections, parasitic diseases, protozoan diseases, and diseases caused by metazoan parasites.

18. SAXTON, J. A., JR. Nutrition and growth and their influence on longevity in rats. In: MOORE, R. A., ed. *Biological Symposia. Ageing and Degenerative Diseases.* Lancaster, Pa.; Jaques Cattell Press, 1945, pp. 177–96.

Experiments on various series of rats indicated that retardation of growth of rats by restriction of the food intake increased significantly the average life span and retarded the development of inflammatory, neoplastic and degenerative diseases common to old age. It is probable that morphological or chemical changes, occurring with advancing age and favoring development of diseases of old age, are slowed down when the body grows slowly.

19. URBACH, E. AND GOTTLIEB, P. M. *Allergy.* 2nd ed. New York, Grune, 1946, Chapter 6, pp. 83–96.

Allergic signs in guinea pigs, rabbits, dogs, rats, cats, pigeons, rhesus monkeys, horses and cattle are reviewed. Methods for demonstration of anaphylactic shock are described. Anaphylactic manifestations are considered to be a result of an antigen-antibody reaction which takes place in the tissue cells. The mechanism of anaphylactic shock is discussed. Methods of desensitization are described.

20. CHEEVER, F. S. AND MUELLER, J. H. Epidemic diarrheal disease of suckling mice. I. Manifestations, epidemiology, and attempts to transmit the disease. *J. Exptl. Med.* 85: 405–16 (Apr.), 1947.

An extensive study of epidemic diarrheal disease in suckling mice showed that the disease was almost certainly of infectious origin and that its eradication presented greater difficulties than other infections in mice. A definite tendency toward greater susceptibility in first litters as contrasted with subsequent ones was noted.

21. PAPPENHEIMER, A. M. AND ENDERS, J. F. An epidemic diarrheal disease of suckling mice. II. Inclusions in the intestinal epithelial cells. *J. Exptl. Med.* 85: 417–22 (Apr.), 1947.

Intranuclear inclusions were found in 75% of young mice suffering from a spontaneous diarrheal disease. They were confined to the epithelial cells of the small intestine, and to the intestinal and mesenteric lymphadenoid tissue. They were seen only between the 10th and 15th days after birth. In apparently healthy control mice of the same age group, they were found in only 2 of 36 animals (5.5%) and these were in mice from the same room and stock as the diseased animals. When some members of the same colony were bred with 4 other strains from various sources, diarrhea again became prevalent but in 70 mice examined no intranuclear inclusions were found. The question whether the diarrheal disease in this new strain was identical with the one above remained open. (Author's summary modified)

22. FRICK, E. J. Examining a dog's digestive tract. *J. Am. Vet. Med. Assoc.* 112: 234–5 (Mar.), 1948.

After examining the mucous membranes of the lips, mouth and throat and viewing the tonsils and pharynx, a stomach tube is inserted into the mouth and slipped down the esophagus into the

stomach. Fluoroscopy may be used to assist in the diagnosis. Midriff and abdominal region are examined by palpation with the thumb and fingers; the intestinal contents are examined by means of an enema. A microscopic check of the feces should be routine in all cases. Gastric lavage is advisable in certain cases.

23. SLANETZ, C. A. The control of *Salmonella* infections in colonies of mice. *J. Bacteriol.* 56: 771–5 (Dec.), 1948.

A practical method for the control of *Salmonella* infection in breeding colonies of mice has been developed in the feces culture method. An incidence of less than 0.4% of paratyphoid carriers was obtained in a large commercial mouse colony by the individual-mouse single-test method. To maintain a low incidence of *Salmonella* infection in a breeding colony it is necessary to test young adult mice weighing approximately 20 gm prior to mating. Use of weanling mice resulted in a higher percentage of carriers. (Author's summary)

24. KARTMAN, L. Preliminary observations on the relation of nutrition to pediculosis of rats and chickens. *J. Parasitol.* 35: 367–74 (Aug.), 1949.

Seven different vitamin deficiencies were produced in albino rats. When typical avitaminoses were noted, the rats were given an infestation of lice. Rats deficient in vitamin A, thiamin, riboflavin and pantothenic acid maintained a mild pediculosis during the period after infestation or until death while rats fed diets deficient in pyridoxine, folic acid or choline were able to rid themselves of the lice infestation. Controls on a complete ration also eliminated their parasites. No differences in degree of pediculosis were noted in birds exhibiting malnutrition or birds in robust health. Debeaked birds on a normal ration had a significantly higher degree of pediculosis than their nondebeaked coop mates while this correlation was apparent but less significant in the case of malnutrition.

25. MULLIGAN, R. M. *Neoplasms of the Dog.* Baltimore, Williams & Wilkins, 1949, 144 pp.

The book contains the following chapters: Mammary neoplasms; epithelial neoplasms of skin and its appendages; neoplasms of mesenchymal origin and of nerve sheath cells; melanoma; mast cell sarcoma, lymphosarcoma, histiocytoma; neoplasms of endocrine glands; other neoplasms. A technical supplement, listing procedures for the preparation of pathologic specimens for mailing and for fixing, embedding and sectioning tissues, is included.

26. UDALL, R. H. Parasites and their control. In: MCCAY, C. M., ed. *Nutrition of the Dog.* 2nd ed. Ithaca, N. Y., Comstock Pub. Associates, 1949, pp. 298–308.

Measures for the prevention of parasitic infection of dogs and the most frequent types of infection are discussed. Sanitation is the primary requisite in all colonies. In a production colony the female should be freed of all parasites before breeding. Drugs for the treatment and cure of parasitic infections are reviewed.

27. PARISH, H. J. *Notes on Communicable Diseases of Laboratory Animals.* Edinburgh, Livingstone, 1950, 69 pp.

Communicable diseases occurring in the following laboratory animals are described: guinea pig, rabbit, mouse, rat, hamster, ferret, monkey, cat, dog, pigeon, canary. Symptoms, causal organisms, post-mortem findings, treatment and control are discussed in each case.

28. WHITESIDE, W. H. Notes on the common feline diseases as found at the University of Western Ontario. *Proc. Animal Care Panel* 1st Ann. Meeting, Nov. 28, 1950, pp. 40–2.

Diagnosis, symptoms and treatment of the following common feline diseases are described: coryza, pneumonia, gastroenteritis, anorexia, and granulation of the nictitating membrane. (Condensed abstract)

29. CUMMING, C. N. W. Investigations dealing with diagnosis and control. *Proc. Animal Care Panel* 2nd Ann. Meeting, Nov. 29–30, 1951, pp. 50–63.

Environmental factors (spacious quarters, sanitation) and diet seem to be influential in the control of *Salmonella* in mice. Incorporation of aurofac (containing a variety of nutritional components plus Aureomycin) into the diet seemed to raise the resistance of the mice so that, though they still harbored *Salmonella* organisms, they were not affected by them. Genetic selection as well as immunization of breeding stock was of limited value. Chemotherapy and antibiotic therapy failed to eliminate *Salmonella* from the intestines. Bacteriologic tests were useful in diagnosis but did not help to control the disease in large colonies. (19 references)

30. FISHER, L. E. Disease problems and handling of laboratory primates. *Proc. Animal Care Panel* 2nd Ann. Meeting, Nov. 29–30, 1951, pp. 18–25.

Since new arrivals may suffer from change in environment, internal and external parasites, malnutrition and the entire range of infectious diseases, they should be isolated before being added to the existing colony. A tuberculin test and measures for control of parasites are described. Suggestions are made for an adequate diet, treatment of some diseases, sanitation and safe handling.

31. HABERMANN, R. T. Gastrointestinal parasites of laboratory animals. *Proc. Animal Care Panel* 2nd Ann. Meeting, Nov. 29–30, 1951, pp. 36–46.

A 3-yr. study of the incidence of internal parasites in mice, rats, guinea pigs, rabbits and monkeys showed that the common parasitic diseases of mice and rats were coccidiosis, teniasis and oxyuriasis; of guinea pigs, coccidiosis, oxyyuriasis; of monkeys, strongyloidiasis, oesophagostomiasis and balantidiasis. Sulfamethazine was found to be effective for control of coccidiosis in rabbits, phenothiazine for pinworms and heterakids and Pb arsenate for tapeworms. Cockroaches which might contaminate the feed were eliminated by a 2% solution of chlordane.

32. HARDING, H. B. AND COHEN, B. J. An isolation program for monkeys: epidemiological and physical aspects. *Proc. Animal Care Panel* 2nd Ann. Meeting, Nov. 29–30, 1951, pp. 26–35.

Infectious diseases may be transmitted to animals *1*) by immediate or direct contact with a diseased individual, *2*) by contact with fomites, *3*) through food and water, *4*) through contact with contaminated soil, *5*) through the air and *6*) by arthropods. Besides there is the problem of cross infection. Medical aseptic techniques are differentiated from surgical aseptic techniques in planning isolation facilities. A survey of animal isolation facilities is presented. An isolation cage for monkeys to be used for planned infections is described.

33. BAKER, J. A. Control of virus infections in laboratory dogs. *Proc. Animal Care Panel* 3rd Ann. Meeting, Dec. 3–4, 1952, pp. 41–6.

Distemper and infectious hepatitis and measures to control them are discussed.

34. CARNOCHAN, F. G. AND CUMMING, C. N. W. Immunization against *Salmonella* infection in a breeding colony of mice. *J. Infectious Diseases* 90: 242–8 (May-June), 1952.

An attempt was made to determine the effect of immunization in 2 colonies of breeding mice of CFW strain against an epizootic of *Salmonella enteriditis*. Three different vaccines were tested. The results are discussed. Death rates of unvaccinated and vaccinated mice are tabulated and shown graphically.

35. Cass, J. S. Enteric infections in monkeys. *Proc. Animal Care Panel* 3rd Ann. Meeting, Dec. 3–4, 1952, pp. 14–22.

Digestive disorders caused by faulty diet, bacteria, protozoa or worms and prevention and treatment of their disorders are discussed.

36. Christian, J. J. and Ratcliffe, H. L. Shock disease in captive wild mammals. *Am. J. Pathol.* 28: 725–37 (July-Aug.), 1952.

The death of 14 captive wild animals (from the family of Mustelidae, Felidae, Procyonidae and Canidae) from shock disease is reported. All of them died within a few hours to 2 days after having been subjected to minor stress, such as being transferred to new quarters or being disturbed by repairs to adjacent cages. Histologic examination indicated that the immediate cause of death was hypoglycemia caused by adrenopituitary exhaustion through inactivity. Thus, shock disease in the captive wild animals resulted from an adjustment to inactivity while in free wild animals the disease develops when environmental demands exceed maximum native capacities.

37. Eaton, O. N. Abnormalities in the mouse. *J. Heredity* 43: 159–66 (July-Aug.), 1952.

Tail anomalies, polydactylism and syndactylism and hydrocephalus in a colony of mice maintained by the Bureau of Animal Industry are described. (28 references)

38. Gambles, R. M. *Myocoptes musculinus* (Koch) and *Myobia musculi* (Schranck), two species of mite commonly parasitizing the laboratory mouse. *Brit. Vet. J.* 108: 194–203, 1952.

Two fur-frequenting parasites of the mouse, *Myocoptes* and *Myobia*, are described and illustrated in both the adult and immature stages. *Myocoptes* is capable of setting up symptoms of mange in the laboratory white mouse when the normal host-parasite relation is upset. The literature is reviewed. (Author's summary)

39. Gledhill, A. W. and Rees, R. J. W. A spontaneous enterococcal disease of mice and its enhancement by cortisone. *Brit. J. Exptl. Pathol.* 33: 183–9 (Apr.), 1952.

An enterohepatitis of mice due to an enterococcus is described. The spontaneous disease was associated with a serious morbidity and mortality in the breeding colony. The disease could be produced experimentally by i.p. or i.v. inoculation of the organism or by feeding it to mice. The susceptibility to the experimental disease was increased by cortisone. The organism is not known to cause disease in any other species of animal.

40. Griffin, C. A. A study of prepared feeds in relation to *Salmonella* infection in laboratory animals. *J. Am. Vet. Med. Assoc.* 121: 197–200 (Sept.), 1952.

After an explosive outbreak of infection with *Salmonella newport* in 2 guinea pig and later in mouse-breeding colonies, the presence of *Salmonella* was revealed in dog feed and rabbit and guinea pig pellets. This is believed to be the 1st report of the recovery of viable *Salmonella* from prepared feeds.

41. Griffin, C. A. Respiratory infections among rabbits. Control and eradication. *Proc. Animal Care Panel* 3rd Ann. Meeting, Dec. 3–4, 1952, pp. 3–13.

Epizootic or enzootic respiratory infections in the rabbit caused by *Bacterium bronchisepticum*, *Pasteurella lepiseptica*, *Staphylococcus aureus*, and hemolytic streptococcus are discussed. Diagnosis has been based on presumptive tests of lung or other cultures taken at necropsy and on nasal cultures from living and dead animals. Emphasis is placed on eradication through the development of solated new groups from animals selected after a series of nasal cultures. Bacteriologic examinations are repeated until there is a relative assurance that all infected animals have been removed. (Condensed from author's summary)

42. Merck & Co. *Streptomycin and Dihydrostreptomycin. Their Practical Application in Veterinary Medicine*. Rahway, N. J., Feb. 1952, 20 pp.

The properties of streptomycin and dihydrostreptomycin, their specific indications, dosage for various animal species (such as mouse, rat, cat, dog, guinea pig, rabbit, monkey, cattle, swine, horse, fowl) and methods of administration are discussed.

43. Meyer, K. F. and Eddie, B. Disease problems in guinea pigs. *Proc. Animal Care Panel* 3rd Ann. Meeting, Dec. 3–4, 1952, pp. 23–40.

Frequency of occurrence, symptoms, mortality, necropsy findings, causal organisms and control are discussed for bacterial diseases (salmonellosis, streptococcus infections, pneumonia, *Klebsiella* pneumonia, pseudotuberculosis, bronchisepticum, pasteurellosis, cervical adenitis, pseudomonas infection, tuberculosis), viral diseases (virus pneumonia, salivary gland disease, lymphocytic choriomeningitis), diseases of unknown, possibly virus etiology (wasting disease, Slanetz disease, enterohepatitis), protozoan diseases (toxoplasmosis, etc.), and diseases caused by ectoparasites (lice).

44. Page, K. W. The ectoparasites of laboratory and domestic animals. *J. Animal Technicians Assoc.* 3: 34–6 (Sept.), 1952.

The life history, transmission and control of fleas, lice, mites and ticks in regard to laboratory and domestic animals is described.

45. Sarles, M. P. and Vandegrift, W. B. Chronic oral toxicity and related studies on animals with the insecticide and pyrethrum synergist, piperonyl butoxide. *Am. J. Trop. Med. Hyg.* 1: 862–83 (Sept.), 1952.

Piperonyl butoxide was found to be a material of a relatively low order of toxicity for the tested warm-blooded animals. There was relatively little difference between sexes and between species of animals (rats, dogs, monkeys, goats) in susceptibility to this material, and no indication of cumulative toxic effect upon the 2nd and 3rd generations of rats fed food containing up to 10,000 ppm of piperonyl butoxide.

46. Young, W. A. Feline restraint and medication. *J. Small Animal Med.* 1: 208–14 (Nov.), 1952.

Treatment of wounds, dentistry and fractures in cats are discussed.

47. Coffin, D. L. *Manual of Veterinary Clinical Pathology*. 3rd ed. Ithaca, N. Y., Comstock Pub. Associates, 1953, 322 pp.

The book contains the following chapters: Microscopic techniques; collecting, packing and shipping of specimens; parasitologic and urine examinations; hematology; diagnostic methods in

bacterial, mycotic, virus, protozoan disease; fertility examinations; formulas and staining techniques. The chapter on hematology includes hematologic techniques as well as tables on normal values of cellular elements in the blood of the horse, cattle, sheep, goat, swine, dog, cat, monkey, mink, rabbit, rat, guinea pig, mouse, chicken, frog.

48. Cook. R. Murine mange: The control of *Myocoptes musculinus* and *Myobia musculi* infestations. *Brit. Vet. J.* 109: 113–6 (Mar.), 1953.

The occurrence of 2 distinct parasitic manges of mice is described. The condition caused by *Myocoptes musculinus* may be kept under control by the judicious use of benzene hexachloride, and the other, caused by *Myobia musculi*, by dipping affected mice in a dilute solution of tetraethylthiuram monosulfide. (Condensed from author's summary)

49. Deringer, M. K., Dunn, T. B. and Heston, W. E. Results of exposure of strain C3H mice to chloroform. *Proc. Soc. Exptl. Biol. Med.* 83: 474–9 (July), 1953.

Exposure of strain C3H mice to air containing approx. 5 mg of chloroform/l. for 1, 2, or 3 hr. resulted in lesions of the kidneys of all of the males but in none of the females. Histologic details of this lesion are described. The lesion found in the male animals in this experiment was similar to that exhibited by the males of strains C3H, $C3H_f$, A, and HR, some of which died immediately after an accidental exposure to chloroform and some in the months following the exposure. A genetic difference was apparent in that whereas strains C3H, $C3H_f$, A, and HR were susceptible, strains C57BL, C57BR/cd, C57L, and ST were resistant to the accidental exposure. (Author's summary)

50. Fuentes, C. A., Schwarz, J. and Aboulfia, R. Some aspects of the pathogenicity of *Candida albicans* in laboratory animals. *Mycopathol. et Mycol. Appl.* 6: 176–81, 1953.

A study of nervous and hemorrhagic signs of experimental moniliasis and data on the comparative susceptibility of rabbit, rat, mouse and guinea pig to *C. albicans* are presented. Paresis, ataxia, choreatic movements, unilateral muscle contractures, etc., were observed in every animal species tested. Rats showed also epistaxis and bloody eyes. Susceptibility is most outspoken in the following order: rat, rabbit, guinea pig, mouse. Rats showed a special selectivity for prostatic localization which was absent in the other species. The possibility of toxic endothelial damage is mentioned. (Author's summary modified)

51. Gray, E. H. and Hazleton, L. W. Control rats in chronic feeding experiments. *Federation Proc.* 12: Abstr. No. 1072 (Mar.), 1953.

Long-term feeding studies were carried out with rats and food consumption, body weight, mortality and observations of abnormal behavior or appearance were recorded each week. The incidence of tumors was studied with emphasis on frequency of malignancies. A basis was provided for the establishment of indices of intoxication due to compounds added to the normal diet.

52. Horváth, Z. (Follicular keratosis in rabbits.) *Acta Vet. Hung.* 3: 91–5, 1953.

The signs and histology of follicular keratosis in a rabbit's ear and on the shoulders are described. The lesions formed hard projections 20 mm long. Attempts at transmitting the infection and at treatment failed. Four photographs of lesions are shown. (*Vet Bull.* 23: Abstr. No. 2664, 1953)

53. Jenkins, D. W. Epidemiology and transmission of rabbit myxomatosis. *Proc. Animal Care Panel* 4th Ann. Meeting, Dec. 2–3, 1953, pp. 93–7.

The spread of rabbit myxomatosis is described. Transmission occurs almost entirely by biting arthropods, especially mosquitoes; contact infection may take place under some conditions. Infected rabbits display lack of appetite, inflamed eyes with a purulent discharge, and a rough coat. The mortality rate may be 100%. Suitable quarantine should be established and maintained.

54. Kirk, H. *Index of Diagnosis (Clinical and Radiological) for the Canine and Feline Surgeon.* 4th ed. Baltimore, Williams & Wilkins, 1953, 667 pp.

The most common symptoms are discussed in alphabetical order. General methods of diagnosis are listed.

55. Merck & Co., *Coccidiosis. Annotated Bibliography.* Rahway, N. J., 1953, 86 pp.

The literature on coccidiosis for the past 20 yr. in birds (poultry, game birds), large mammals (cattle, sheep, swine), and small mammals (dogs, cats, rabbits, fur-bearing and laboratory animals) is abstracted. A table is appended listing the various substances used for treating or preventing coccidiosis.

56. Rucker, R. R., Whipple, W. J., Parvin, J. R. and Evans, C. A. A contagious disease of salmon possibly of virus origin. *U. S. Fishery Bull.* No. 76, 1953, pp. 35–46.

A disease, possibly of virus origin, is described which affected blueback salmon and kokanee fingerlings (*Oncorhynchus nerka*), but did not infect fingerlings of the Chinook salmon (*O. tshawytscha*), silver salmon (*O. kisutch*), or cutthroat trout (*Salmo clarki clarki*). Therapeutic measures, consisting of sulfonamides, antibiotics, and external disinfectants, failed to control the disease. Rigid sanitary measures limited spread of the infection in some cases. (Condensed from author's summary)

57. Schneider, H. A. Nutrition and resistance to infection. *Borden's Rev. Nutrition Research* 14: 17–32 (Mar.-Apr.), 1953.

Literature references are quoted to illustrate the relationship of nutrition and susceptibility to infections. Thus, for instance, riboflavin decreases the severity of *Plasmodium lophurae* infections in chicks. A short-term deficiency of pyridoxine reduced the severity of mouse pneumonitis. In mouse salmonellosis, withholding fat from the diet results in increased survivorship, adding fat in decreased survivorship.

58. Shubik, P. and Ritchie, A. C. Sensitivity of male dba mice to the toxicity of chloroform as a laboratory hazard. *Science* 117: 285 (Mar. 13), 1953.

Fifty mice out of 55 male dba mice died within 6 days after another group of mice housed in the same cage had been sacrificed by means of chloroform. Fifty-five female dba mice and a considerable number of mice of strains A, C, C3H and CAF_1 hybrid of both sexes which had been kept on the same rack remained healthy. The toxicity of chloroform to male dba mice was confirmed experimentally. The unusual laboratory hazard of chloroform to male dba mice is pointed out.

59. Bacigalupo, J. and Roveda, R. J. *Demodex caviae* n.sp. *Rev. med. vet.* (Buenos Aires) 36: 149–53, 1954.

In the course of an investigation of trichinosis in guinea pigs a demodex mite was found in the muscular tissue. Its morphology

is described and the designation *Demodex caviae*, Roveda—Bacigalupo, 1953, is suggested. (*Vet. Bull.* 27: Abstr. No. 2434 1957)

60. BITTNER, J. J. Mammary cancer in mice observed in different laboratories and during the war period. *Proc. Am. Assoc. Cancer Research* 1: 6 (Apr.), 1954.

A higher incidence of spontaneous mammary cancer and an earlier average cancer age was found in breeding female mice of the Z (C_3H) stock born in 1948 than in those born from 1943–6 in the same laboratory. It was assumed that this phenomenon was due to some alteration in the hormonal mechanism caused by a change of diet during the war.

61. BLACK, W. G., SIMON, J., KIDDER, H. E. AND WILTBANK, J. N. Bactericidal activity of the uterus in the rabbit and the cow. *Am. J. Vet. Research* 15: 247–51 (Apr.), 1954.

Comparisons were made of the numbers of bacteria recoverable from the uteri of estrous, spayed, and pseudopregnant rabbits inoculated 24 hr. previously with known concentrations of *Escherichia coli*. Estrous and spayed females exhibited a high degree of bactericidal activity; ligation of the cervices in these animals tended to increase the number of surviving bacteria by preventing natural drainage. Bactericidal or bacteriostatic activity was practically nonexistent in pseudopregnant females. The same technique was employed in comparing the uterine bactericidal activity of luteal-phase cows of normal and impaired fertility. "Repeat-breeding" cows generally exhibited a greater defense toward bacterial infection than did "first-service" animals, suggesting a possible cause of their lowered fertility. (Author's summary)

62. CRABB, E. D. AND KELSALL, M. A. A myxosarcoma HS-5, transplantable in hamsters. *Proc. Am. Assoc. Cancer Research* 1: 10 (Apr.), 1954.

A tumor which had started spontaneously in a male Syrian hamster in an inbred colony was transplanted to 20 hamsters. A report is given of the development.

63. DETTLI, L., CAPELLER, D.V. AND BUCHER, K. Die Verwendung von Rindererythrocytensuspensionen für Kreislaufexperimente an der Katze. (The use of bovine erythrocyte suspensions for experiments on circulation in cats.) *Helv. Physiol. et Pharmacol. Acta* 12: 90–7, 1954.

The transfusion into cats of blood from other cats affects the pulmonary circulation of the animals. The possible reasons for this phenomenon are discussed. However, a suspension of bovine erythrocytes in periston (polyvinylpyrrolidone) was well tolerated.

64. FLYNN, R. J. Mouse mange. Part I: General considerations. *Proc. Animal Care Panel* 5th Ann. Meeting, Dec. 1–2, 1954: 96–105.

Clinical appearance, diagnosis, incidence and control of myobic and myocoptic acariasis and other mite infestations in mice are reviewed. Acaricide screening experiments with CF_1 female mice showed that of the substances tested only Aramite®-15W had a broad effective non-toxic dose range.

65. GUERIN, M. *Tumeurs Spontanées des Animaux de Laboratoire: Souris, Rat, Poule.* (*Spontaneous Tumors in Laboratory Animals: Mouse, Rat, Chicken.*) Paris, A. Legrand, 1954, 215 pp.

A detailed description and an extensive bibliography on tumors in mice, rats and chicken is presented. 130 microphotographs are included.

66. HABERMANN, R. T., WILLIAMS, F. P., JR. AND THORP, W. T. S. Identification of some internal parasites of laboratory animals. *U. S. Public Health Serv. Publ.* No. 343, 1954, 29 pp.

Photomicrographs of helminth eggs and of protozoa are given and the incidences of the different parasites, based on findings from 6,209 laboratory animals (mice, rats, guinea pigs, rabbits, monkeys, cats and dogs) are reported. Of the several methods used for diagnosis of parasitic infestations in laboratory animals the direct smear and the salt flotation centrifugation method are discussed in detail. The kinds of intestinal parasites in the cages of mice, rats, hamsters and guinea pigs are determined by the composite sample technique. Morphology, life cycle, incidence, pathology, diagnosis, control and treatment are given for the following parasites: tapeworm, roundworm and other nematodes of mouse and rat; protozoa of mouse and rat; roundworm and protozoa of the guinea pig, coccidiosis in rabbit, roundworms and protozoa in rhesus monkey; tapeworm, roundworm and protozoa in dog and cat.

67. HARDY, A. V. Problems in the control of infectious diseases in a large colony of primates. *Proc. Animal Care Panel* 5th Ann. Meeting, Dec. 1–2, 1954: 16–21.

Bacteriological, parasitological, virological, pathological and epidemiological observations are reported; methods of control and therapy are discussed. It is stated in the discussion that an intramuscular daily dose of 5 mg Tetracyn/lb. body weight is at the present the therapeutic method of choice.

68. JONES, T. C. AND GLEISER, C. A. ed. *Veterinary Necropsy Procedures.* Philadelphia, Lippincott, 1954, 136 pp.

The book contains the following chapters: Importance of necropsy; general principles of necropsy procedure (time, place, equipment for necropsy, disposal of carcass, euthanasia); necropsy procedures for horse, cattle, sheep, swine, dog, cat, chicken and other birds, and laboratory and wild animals; preparation of necropsy protocols and of laboratory and parasitologic specimens; suggestions for histologic diagnosis of various diseases.

69. KIRK, H. *Index of Treatment in Small-Animal Practice.* 3rd ed. Baltimore, Williams & Wilkins, 1954, 888 pp.

In part I the following therapies are discussed: actino-, electro-, chemo-, hormone-, vaccine- and serum, vitamin-, barbiturate-therapy; antiseptics, anesthetics, antihistamines. In part II an index of therapeutics is given. Part III deals with handling and restraint, administration of medicine, nursing and feeding the sick, foods and feeding, disinfection, euthanasia, rat extermination. Detailed posological tables are included.

70. RATCLIFFE, H. L. Disease control and colony management of infrahuman primates at the Philadelphia Zoological Garden. *Proc. Animal Care Panel* 5th Ann. Meeting, Dec. 1–2, 1954: 8–15.

Methods to exclude respiratory disease in colonies of primates, by testing each new animal for tuberculosis and quarantining it for a certain period are discussed. The importance of an adequate diet and of ample space and facilities for control of diseases is pointed out. A healthy rhesus monkey, weighing 4–6 kg, should have a hemoglobin and leukocyte count of 12–14 gm/100 ml and 5,000–10,000/cu mm, respectively, and should be able to run 0.5 mi. in about 2 min. without obvious distress.

71. RISER, W. Disease problems in the management of the cat colony: part II. *Proc. Animal Care Panel* 5th Ann. Meeting, Dec. 1–2, 1954: 87–91.

Pathological changes occurring in feline panleukopenia and pneumonitis and diagnostic tests for these diseases are discussed.

72. RUNNELLS, R. A. *Animal Pathology*. 5th ed. Ames, Iowa State College Press, 1954, 718 pp.

In part I, the etiology of diseases, disturbances of development, nutrition, growth of cells, cell metabolism and circulation, tumors and defenses of the body are discussed. In part II the pathology of the following systems is treated: cardiovascular, hematopoietic, respiratory, digestive, urinary, genital and nervous. Part III deals with the special pathology of infectious diseases (bacterial, fungus, virus), and part IV with the pathology of food-deficiency diseases. In the appendix techniques of necropsy of the horse, ruminant, dog, cat and swine are described.

73. SCHWARZ, J. The deep mycoses in laboratory animals. *Proc. Animal Care Panel* 5th Ann. Meeting, Dec. 1–2, 1954: 37–70.

Two indirect methods for the diagnosis of fungus diseases are described, the skin test and the serologic tests. The following deep fungus diseases in laboratory animals are reviewed: blastomycosis, histoplasmosis, coccidioidomycosis, haplomycosis, cryptococcosis, sporotrichosis, actinomycosis, Haverhill fever, moniliasis, chromoblastomycosis, aspergillosis, dermatomycoses.

74. WOLF, N. S. Disease problems in the management of the cat colony: part I. *Proc. Animal Care Panel* 5th Ann. Meeting, Dec. 1–2, 1954: 81–6.

The most prevalent diseases occurring in cat colonies are virus disease, feline pneumonitis, and parasitic diseases. The following measures for prophylaxis are proposed: quarantine of incoming cats for 10–14 days; easily sterilizable cages without cross ventilation and providing ample space; sterilization of water and food dishes.

75. BENBROOK, E. A. AND SLOSS, M. W. *Veterinary Clinical Parasitology*. 2nd ed. Ames, Iowa State College Press, 1955, 206 pp.

The following laboratory techniques for the diagnosis of parasitism are discussed: *1*) Fecal examination, *2*) examination for mites of the skin and the internal organs, *3*) diagnosis of louse infestations. Animals included are horses, cattle, sheep, goats, swine, dogs, cats, birds, rabbits, guinea pigs, rats, mice, and others. The book contains 271 illustrations and an extensive bibliography.

76. CHABAUD, M. A., SÉRIÉ, C. AND ANDRAL, L. Électrophorèse et diagnostic de la rage. (Electrophoresis in the diagnosis of rabies.) *Ann. inst. Pasteur* 88: 420–34 (Apr.), 1955.

Paper electrophoresis of serum proteins may be of considerable value in the early diagnosis of rabies in certain animals, particularly the dog. In rabies-affected dogs, horses, donkeys, cattle and cats, the electrophoretic patterns of the serum proteins revealed a marked increase in the α_2-globulin fraction and a slight increase of serum albumins. In rabbits, guinea pigs, rats, mice and sheep, only 40% of the rabies-affected animals showed such an increase which was always smaller than in the dog. In pseudorabies a marked increase of the β_1-globulin fraction was noted in the dog.

77. EYLES, D. E. AND COLEMAN, N. The effect of sulfadimetine, sulfisoxazole, and sulfapyrazine against mouse toxoplasmosis. *Antibiotics & Chemotherapy* 5: 525–8 (Oct.), 1955.

Sulfadimetine and sulfisoxazole were ineffective against mouse toxoplasmosis except at very high dosages. Sulfapyrazine, on the other hand, showed outstanding activity. This compound is the most active of the sulfonamides tested to date by this laboratory. (Condensed from author's summary)

78. EYLES, D. E. AND COLEMAN, N. An evaluation of the curative effects of pyrimethamine and sulfadiazine, alone and in combination, on experimental mouse toxoplasmosis. *Antibiotics & Chemotherapy* 5: 529–39 (Oct.), 1955.

Mice of the NIH general purpose strain were inoculated i.p. with counted numbers of *Toxoplasma* organisms. The drugs to be tested were administered with the diet. Both pyrimethamine and sulfadiazine when administered just after inoculation with *Toxoplasma* possessed curative properties; the amount necessary for cure was proportionate to the size of the inoculum. The median effective curative dose for 20,000 and 2,000 inoculum, respectively, was: pyrimethamine 22.5 and 8 mg % of the diet, sulfadiazine 98 and 18 mg %. When the drugs were administered jointly, less than 16 mg % sulfadiazine plus 0.55 mg % pyrimethamine were curative for an inoculum of 20,000 organisms.

79. FLYNN, R. J. Control of ectoparasites in mice. *Proc. Animal Care Panel* 6: 71–91, 1955.

A survey of commercially produced laboratory mice available in this country has shown that almost all are infested with more than one of the following ectoparasites: *Myobia musculi* Schrank, *Myocoptes romboutsi* Van Eyndhoven, *Myocoptes musculinus* Koch, *Radfordia affinis* Poppe, *Psorergates simplex* Tyrrell, and *Polyplax serrata* Burmeister. Morphological illustrations, the probable associated pathology, and a method of eradication of these ectoparasites has been presented. Nonparasitic skin disorders of ectoparasite-free mice are now being studied. (Author's summary)

80. GLEDHILL, A. W. AND NIVEN, J. S. F. Latent virus as exemplified by mouse hepatitis virus (MHV). *Vet. Revs. and Annotations* 1, Pt. 2: 82–90 (Oct.), 1955.

The fact that mice latently infected with mouse hepatitis virus (MHV) develop active infection if they are inoculated with *Eperythrozoon coccoides*, demonstrates the usefulness of mice, the natural host of MHV, for investigating latent virus.

81. HALLORAN, P. O. A Bibliography of References to Diseases in Wild Mammals and Birds. *Am. J. Vet. Research* 16, Pt. 2: 1–465 (Oct.), 1955.

References to rabbits, hamsters and rats have been deliberately omitted from this bibliography. The material is arranged as follows: Infectious diseases and parasites; skin, mucous membrane, mammae; musculoskeletal, respiratory, cardiovascular, hemic and lymphatic, digestive, urinary, genital, endocrine and nervous systems; special senses; tumors; anatomy and anatomical anomalies; general and miscellaneous (longevity, care and management, nutrition, albinism, anesthetics, anthelmintics, physiology).

82. HULL, T. G. *Diseases Transmitted from Animals to Man*. 4th ed. Springfield, Ill., C. C. Thomas, 1955, 720 pp.

The book contains 3 sections. Section 1 is concerned with the following diseases of domestic animals, birds, rodents and wild animals: tuberculosis, anthrax, brucellosis, vibriosis, glanders,

XUM

swine erysipelas, *Salmonella* food infections, listeriosis, rabies, psittacosis, vesicular stomatitis, pox diseases, milker's nodules, contagious ecthyma of sheep, Newcastle disease, lymphadentitis and lymphoreticulosis, pseudotuberculosis, septicemia, *Pasteurella multocida* infection, arthropod-borne viral encephalitides, Rift Valley fever, milk sickness, parasitic and fungal disease. Section 2 discusses plague, tularemia, leptospirosis, rat-bite fever, endemic relapsing fever, murine typhus fever, Rocky Mountain spotted fever, tsutsugamushi disease, Q fever, rickettsialpox, jungle yellow fever, lymphocytic choriomeningitis. In section 3 the relation of human and animal diseases is discussed. Among animals mentioned the most important are cattle, chicken, horse, swine, sheep, dog, cat, rat, mouse, monkey, bat, goat, ferret, guinea pig, hamster, opossum, mink, pigeon, rabbit.

83. *Merck Veterinary Manual; A Reference Handbook of Diagnosis and Therapy for the Veterinarian.* Rahway, N. J., Merck & Co., 1955, 1385 pp.

The manual provides information on the diagnosis and treatment of diseases of animals. Part I is devoted to diseases of large and small animals; diagnosis, therapy, pathology, epizootiology and surgical procedures are described. It is divided into the following sections: allergy; blood, lymphatic and cardiovascular; breeding and obstetrics; digestive system; endocrine; eye and ear; genitourinary; infectious diseases; metabolic disturbances; musculoskeletal; neoplasms; nervous system; nutrition; parasitic diseases; respiratory; skin and connective tissue. Part II is concerned with toxicology, part III with diseases of poultry, part IV with health and disease problems of animals kept in laboratories or otherwise confined. The addendum of part V lists various techniques and diagnostic methods and includes tables of body temperature and hemograms for a number of animals.

84. CARPENTER, K. J. Obesity in laboratory animals. *J. Animal Technicians Assoc.* 7: 35–6 (Sept.), 1956.

The animal protects itself from obesity by some relay mechanism operating through the brain which restricts the desire for food. When the ventromedial hypothalamic region of the brain is damaged by electric stimulations or by injections of goldthioglucose, the animals have lost any satiety mechanism and become obese simply by overeating without any metabolic disturbance. Obesity may also occur in some strains by hereditary characters. This condition is linked with a recessive gene. The homozygous obese animals will not reproduce while, by breeding of their nonobese litter mates, "1 in 4" of the offspring is again obese. This obesity is characterized by a hyperglycemic syndrome. There is also an obesity associated with the dominant gene for "yellow coat" character in mice, with a syndrome different from either of the 2 described above.

85. CAVIER, R. Les propriétés anthelminthiques de quelques esters de l'acide cinnamique et de dérivés voisins. (Anthelmintic properties of esters of cinnamic acid.) *Bull. soc. pathol. exotique* 49: 631–6 (July-Aug.), 1956.

n-Butyl cinnamate given to mice at 100 mg/kg gave 100% efficiency against oxyurids. It proved successful for oxyuriasis in young children and being nontoxic it has a place in the treatment of such infestation. (*Vet. Bull.* 27: Abstr. No. 2129, 1959)

86. COLE, C. R., *Chairman*, KOPROWSKI, H. AND NIGRELLI, R. F. Some protozoan diseases of man and animals: Anaplasmosis, babesiosis, and toxoplasmosis. *Ann. N. Y. Acad. Sci.* 64, Art. 2: 25–277 (July), 1956.

Anaplasmosis, babesiosis and toxoplasmosis, and their diagnosis, treatment and prevention are discussed.

87. COOK, R. Murine ear mange: The control of *Psorergates simplex* infestation. *Brit. Vet. J.* 112: 22–5 (Jan.), 1956.

An outbreak of ear mange in 2 mouse colonies is described. The causal agent was a mite, *Psorergates simplex*. The disease was cured and eradicated by the use of dibutyl phthalate. Three other agents used were without value. (Author's summary)

88. COTCHIN, E. *Neoplasms of the Domesticated Mammals.* Farnham Royal, Buckshire, England, Commonwealth Agricultural Bureaux (*Review Series* No. 4), 1956, 100 pp.

Tumors in the horse, ox, sheep, pig, dog and cat are discussed. The book contains chapters on neoplasms of skin and subcutaneous tissues, mammary gland, musculoskeletal, respiratory, cardiovascular, hemopoietic and lymphatic, urinary, male and female genital, endocrine and nervous systems, eye and ear.

89. CROSS, R. F. AND FOLGER, G. C. The use of malathion on cats and birds. *J. Am. Vet. Med. Assoc.* 129: 65–6 (July 15), 1956.

Malathion proved nontoxic to cats when used as a 0.2% dip, as a 25% powder or given per os in a dose of 2 gm of 25% powder. Malathion poisoning was produced by dipping a 4-mo.-old kitten in a 50% emulsion. It was nontoxic for parakeets and cockateels when placed on the floor of the nest.

90. DAVIS, R. K., STEVENSON, G. T. AND BUSCH, K. A. Tumor incidence in normal Sprague-Dawley female rats. *Cancer Research* 16: 194–7 (Mar.), 1956.

A tumor incidence of 57% was observed in 150 female rats allowed to live out their life span as normal control animals on standard laboratory chow. One hundred similar rats on a special fat-rich diet developed an 80% tumor incidence. Of the tumors observed, 95% involved mammary gland tissue, 12% were of a malignant type, and 87% appeared after the rats were 540 days of age; the mean life span after a tumor was first observed was 140 days. Related studies with a smaller number of animals indicated that male rats of the same strain were 5 times less susceptible to tumor formation than females. However, 3 of 4 tumors that were examined histologically in the males were classified as malignant. The mean life span of normal female Sprague-Dawley rats in this laboratory was 760 ± 21 days, with individuals ranging in life span from 193 to 1100 days. (Author's summary)

91. DICK, G. W. A., NIVEN, J. S. F. AND GLEDHILL, A. W. A virus related to that causing hepatitis in mice (MHV). *Brit. J. Exptl. Pathol.* 37: 90–8 (Feb.), 1956.

A murine hepatitis virus was recovered from mice which had been inoculated with serum from a human case of hepatitis. This murine virus differs from the known murine strain in its greater virulence for weaning mice and in producing ascites in older mice. (From author's summary)

92. ENTICKNAP, J. B. The effect of reduction of bacterial infiltration by aureomycin on the normal alimentary lymphoid tissue of the rabbit. *J. Comp. Pathol. Therap.* 66: 102–8 (Apr.), 1956.

Treatment with 10 mg aureomycin/kg in rabbits reduced the amount of bacterial infiltration normally present in the intestinal lymphoid tissue. This reduction in bacteria was accompanied by a marked reduction in the bulk of the lymphoid tissue. Spleen and thymus were not affected. (Condensed from author's summary)

93. ENTICKNAP, J. B. Survival of normal rabbits after appendectomy. *Nature* 178: 750–1 (Oct. 6), 1956.

A small controlled survival experiment on stock adult albino rabbits showed that appendectomy did not curtail the immunological or nutritional functions of the animal.

94. FANKHAUSER, R. La toxoplasmose chez l'animal. (Toxoplasmosis in animals.) *Arch. suisses neurol. et psychiat.* 77: 195–207, 1956.

Signs and symptoms and histological findings of the organs and the nervous system in canine toxoplasmosis are reported.

95. FROST, R. C. Cholecystography and rupture of the diaphragm in small animals. *Vet. Record* 68: 1014–5 (Dec.), 1956.

A technique for cholecystography in small dogs and cats is described. In all cases the gall bladder was visible and best seen at 13 hr. after oral administration of phenobutiodil. The drug is contraindicated in acute nephritis, acute gastrointestinal disorder and possibly jaundice.

96. FULLER, J. L. The inheritance of structural defects in dogs. *M. S. U. Veterinarian* 16, No. 2 (Winter), 1956, 7 pp.

Some case studies, such as blindness in collies, harelip in boxers and subluxation in German shepherds, are reported and modes of inheritance and inbreeding are discussed.

97. GOFFE, A. Infections in laboratory monkeys. *Lab. Animals Bureau, M. R. C. Lab., Collected Papers* 4: 29–35, 1956.

The usefulness of monkeys as laboratory animals is pointed out. Since the majority of infections in laboratory monkeys are acquired before they reach the laboratory, control measures are suggested for their trapping, holding and transporting. Some common infections of bacterial (tuberculosis, dysentery, pneumonia) and viral nature (poliomyelitis, "B-", lymphocytic choriomeningitis and Simian viruses) are discussed. (Author's summary)

98. GOLDSTEIN, J. AND SCOTT, M. L. An electrophoretic study of exudative diathesis in chicks. *J. Nutrition* 60: 349–59 (Nov.), 1956.

Paper electrophoretic analyses of the proteins in the plasma of chicks, which received a semipurified diet with and without vitamin E, and of exudates of the vitamin E-deficient chicks showed a decrease in the percentage of total protein of chicks suffering from exudative diathesis. Significant quantitative differences were found in the percentage of total protein and A/G ratios. Chicks on a stock ration showed a much higher A/G ratio than corresponding chicks of equivalent age on the basal experimental diet supplemented with a high level of vitamin E. D-α-Tocopheryl acetate orally administered produced complete recovery of chicks suffering from exudative diathesis.

99. GORDON, R. F. Control of disease in laboratory poultry. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 4: 45–56, 1956.

Egg-borne infections of baby chicks and protozoal and respiratory infections of growing stock are discussed. The approach to the control of egg-borne infections is by detection and removal of carriers from the breeding stock, removal of infection from the egg shell, hygiene of the incubator and hatchery and therapy. Procedures of treatment of baby chicks and growing stock are reviewed. (25 references)

100. GORRILL, R. H. Spinning disease of mice. *J. Pathol. Bacteriol.* 71: 353–8, 1956.

Spinning disease in Swiss white mice No. 1 strain was produced by intravenous injection of *Pseudomonas pyocyanea*, mycobacteria and *Nocardia sebivorans*. Administration of *Nocardia* by the intraperitoneal route never caused spinning even when given in doses that killed more than 50% of the experimental mice. The only lesion common to infection with this species of bacteria was inflammation of the inner ear. Spinning disease is considered to be different from rolling disease.

101. GRICE, H. C., GREGORY, E. R. W. AND CONNELL, M. R. E. Diagnosis of middle and inner ear disease in rats. Food and Drug Lab. Dept. Natl. Health and Welfare, Ottawa, Ont., mimeo, 1956, 5 pp.

A roentgenographic method for diagnosing middle and inner ear infections in the live rat is described. The method permits the use of noninfected breeders in a middle and inner ear disease eradication program. (Author's summary modified)

102. GUENTHER, F. Erbliche Entwicklungsanomalien des äusseren Keimblattes beim Kaninchen. Keratose—Hypotrichose— Augenleiden. (Hereditary developmental anomalies of the ectoderm in rabbits. Keratosis, hypotrichosis, eye diseases.) *Berlin. u. Münch. tierärztl. Wochschr.* 69: 214–5, 1956.

Keratosis, hypotrichosis and eye diseases occurring in short-haired rabbits are described. Prolonged vitamin A deficiency over many generations may be the cause of these genetic diseases.

103. HAJSIG, M. AND STILINOVIĆ, Z. Zapažanja o saharomikozi kunića. (*Saccharomycopsis guttulata* infection in rabbits.) *Vet. Arhiv.* 26: 81–5, 1956.

S. guttulata was isolated from feces of rabbits in a large rabbitry. Clinically there was anorexia, bloat, catarrhal inflammation of the upper respiratory mucosa and the conjunctiva. Droppings were slimy and stuck together. Treatment with a proprietary methylene blue preparation was successful. The role of vitamin A deficiency as a predisposing factor is considered. The organism grew at 37°C and a pH of 3.5 in a medium consisting of gelatin and 10% glycerol. (*Vet. Bull.* 27: Abstr. No. 1059, 1957)

104. HALLANGER, L. E. AND SCHULTZE, M. O. Development of fatty livers during lactation of rats fed amino acid rations. *J. Nutrition* 60: 25–34 (Sept.), 1956.

The effect of pregnancy and lactation on the lipid content of livers of rats fed adequate rations composed largely of natural products was studied. Rats fed protein-free amino acid rations developed hypertrophied and severely fatty livers under the stress of lactation. After lactation the concentration of liver lipids decreased. When lactation of rats was supported by an adequate diet some hypertrophy of the liver was observed but the lipid content of the liver decreased. (Author's summary)

105. HANSENS, E. J. Chlordane-resistant brown dog ticks and their control. *J. Econ. Entomol.* 49: 281–3 (Apr.), 1956.

From 1948 to 1955, 2% chlordane residual sprays had been used successfully to control brown dog tick, *Rhipicephalus sanguineus*, in a large dog kennel in northern New Jersey, but in 1955 a large infestation developed which could not be controlled with chlordane. In the laboratory, these ticks were found to withstand exposure to 2%–10% chlordane residues. Malathion used as a residual spray at 1% and 2% concentrations gave partial control of these ticks, as did 1% malathion dips of dogs. Dusting dogs with 4% malathion and 1% lindane failed to give control. Lindane gave tick control when applied in the building as a residual spray at

0.25% or 0.5% concentration or applied to dogs as a dip containing 0.045% lindane. (Author's summary)

106. HIRSCH, S. Étude histologique des réactions anaphylactiques au niveau de la circulation pulmonaire du lapin. (Lesions of the pulmonary arterioles in anaphylactic shock in rabbits.) *Compt. rend. soc. biol.* 150: 2266–9, 1956.

Histological examination of the lungs of rabbits in a state of anaphylactic shock revealed a considerable accumulation of leukocytes in the veins. The hypothesis is advanced that the increased anaphylactic pressure is caused by arterial constriction.

107. INGLE, D. J., ALTAMERO, T. L., JR. AND FLORES, V. Weights of tumors in overfed rats. *Cancer Research* 16: 437–8 (June), 1956.

The growth of tumors can be retarded in experimental animals by reduction of food intake. When male Sprague-Dawley rats were implanted either subcutaneously or intramuscularly with Walker carcinoma 256 and overfed with a fluid carbohydrate diet for 10–11 days, a more rapid gain in body weight was noted but the growth of the tumors was not accelerated.

108. INNES, J. R. M., WILSON, C. AND ROSS, M. A. Epizootic *Salmonella enteritidis* infection causing septic pulmonary phlebothrombosis in hamsters. *J. Infectious Diseases* 98: 133–41 (Mar.–Apr.), 1956.

Two separate outbreaks of salmonellosis in golden hamsters, bought from commercial establishments, are reported. Deaths started within a few hours after arrival; mortality reached almost 100%. This fact and the results from experimentally produced infection in mice, hamsters and rabbits confirm the conclusion that the golden hamster is highly susceptible to salmonella. The origin is presumed to be contact with mice and rats in which salmonellosis might be latent. Therefore, hamster breeding should be isolated from other rodents. The course of the disease, pathology and bacteriology of the natural and experimental disease, with photomicrographs of affected organs, are presented. The use of the hamster for the study of phlebothrombosis by experimental infection with *Salmonella* is suggested.

109. INNES, J. R. M., YEVICH, P. AND DONATI, E. J. Note on origin of some fragments of bone in lungs of laboratory animals. *A. M. A. Arch. Pathol.* 61: 401–6, 1956.

Microscopic fragments of bone have been found as a rare event in the air spaces of the lungs of rats, hamsters, a rabbit, and a guinea pig, but not mice. There is no surrounding reaction to the inert foreign bodies and no concomitant pulmonary disease. The "lesions" are not analogous to those in human lungs of some cases of mitral stenosis or to those occasionally seen in the lungs of old dogs. Evidence is presented to show that the origin is from aspirated fish bone particles derived from the powdered dust of pelleted diets, most of which contain some fish meal. (Author's summary)

110. IYER, P. R. K. AND UPPAL, D. R. Salmonellosis in rabbits. A comparison with rinderpest. *Indian Vet. J.* 32: 430–8, 1956.

Both rinderpest and salmonellosis in rabbits produce identical lesions in Peyer's patches. The comparative histopathology of the intestinal lesions of these diseases is described. Splenic enlargement is almost a constant factor in natural cases of salmonellosis in rabbits but this is not noted among lesions produced by lapinized rinderpest virus.

111. LABORATORY ANIMALS BUREAU, M. R. C. LABORATORIES. *Infections in Laboratory Animals.* (*Collected Papers*, vol. 4) London, 1956, 68 pp.

For abstracts see: Goffe, A. P.; Gordon, R. F.; Paterson, J. S.; Salaman, M. H.; Taylor, J. and Atkinson, J. D.; Tuffery, A. A.; Weipers, W. L.

112. LAPAGE, G., ed. Mönnig's Veterinary Helminthology and Entomology. 4th ed. Baltimore, Williams & Wilkins, 1956, 511 pp.

The book discusses the helminth and arthropod diseases of domesticated animals including the parasitic diseases of fur-bearing animals. A special section deals with techniques for collecting and preserving the parasites and with clinical diagnostic methods. A host-parasite list and a bibliography are included.

113. MCGRATH, J. T. *Neurologic Examination of the Dog with Clinicopathologic Observations.* Philadelphia, Lea, 1956, 181 pp.

The text of this book is divided into 2 sections. The 1st section deals with the neurologic examination of the dog, the 2nd is concerned with clincopathologic observations of the nervous disorders of the dog.

114. MERCHANT, I. A. AND PACKER, R. A. *Veterinary Bacteriology and Virology.* 5th ed. Ames, Iowa State College Press, 1956, 850 pp.

The book contains chapters on general biology of microorganisms; infection, resistance and immunity; classification and characteristics of pathogenic bacteria, yeasts and molds; filtrable viruses. Bacteriological techniques and methods used in the study of viruses are described.

115. NORTH, J. D. K. AND SINCLAIR, H. M. Nutritional neuropathy. Chronic thiamine deficiency in the rat. *A. M. A. Arch. Pathol.* 62: 341–53 (Nov.), 1956.

Individual rats showed a wide variation in their ability to survive during thiamin deficiency. Histological tests led to the conclusion that the nervous system of the rat is relatively resistant to the effects of chronic thiamine deficiency but that if the deficiency is of sufficient length and intensity, degenerative changes will occur in the peripheral nerves.

116. PATERSON, J. S. Control of disease in rabbits. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 4: 37–43, 1956.

Figures of annual percentage mortality in rabbits are published for Great Britain and California. Measures for preventing or curing the following diseases are discussed: Vitamin A and D deficiency; protozoan infections (coccidiosis); virus infections (myxomatosis); bacterial (syphilis due to *Treponema, Pasteurella, Salmonella, Listeria*); fungal (ringworm) and parasitic diseases (mange). Biologic environment and sanitation are pointed out as being the most important factors in the control of diseases.

117. PHILLIPS, G. B., BROADWATER, G. C., REITMAN, M. AND ALG, R. L. Cross infections among *Brucella* infected guinea pigs. *J. Infectious Diseases* 99: 56–9 (July–Aug.), 1956.

Significant cross infection occurred when normal guinea pigs were placed as controls in ventilated cages with guinea pigs exposed bodily to aerosol of *Brucella suis*. Cross infection was demonstrated when the control animals were housed with aerosol-exposed animals continuously for 28 days, for the 1st day after

exposure only, and for the 7th day only. When guinea pigs were exposed to large numbers of aerosolized *Bacillus subtilis* spores and held in ventilated cages, spores were detected in the air of the cages for as long as 18 days. (Author's summary)

118. SALAMAN, M. H. Control of ectromelia in mouse colonies. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 4: 19–20, 1956.

The efficacy of vaccination of laboratory mice with sheep lymph as a routine precaution against mouse-pox was studied. It is suggested to vaccinate all mice from outside sources on arrival and all litters born of vaccinated mothers at 5–6 wk. of age. All mice should be revaccinated after 6 months.

119. SCHNEIERSON, S. S. AND PERLMAN, E. Toxicity of penicillin for the Syrian hamster. *Proc. Soc. Exptl. Biol. Med.* 91: 229–30 (Feb.), 1956.

A single subcutaneous or intraperitoneal injection of crystalline penicillin G potassium is toxic for hamsters in proportion to the administered amount. Toxicity is of the delayed type, occurring mostly between the 3rd and 5th day after injection. Author points out that this parallels experience with guinea pigs, in contrast to Swiss mice who tolerate very large doses of penicillin.

120. TAKETA, F., CONSTANT, M. A., PERDUE, H. S. AND PHILLIPS, P. H. Maternal diet and resistance to dental caries in the cotton rat. *J. Nutrition* 58: 519–27 (Apr.), 1956.

The effects of the level of Ca and protein in the maternal diet upon caries susceptibility in the offspring are tabulated.

121. TAYLOR, J. AND ATKINSON, J. D. *Salmonella* in laboratory animals. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 4: 57–66, 1956.

The following aspects of *Salmonella* infection are discussed: clinical, post-mortem lesions, technique of post-mortem examination, control of *Salmonella* infection, *Salmonella* types, epidemiology and origin of infection.

122. TUFFERY, A. A. Epidemiology and laboratory mice. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 4: 7–17, 1956.

The factors influencing epidemics are reviewed. The two main principles in the intelligent control of disease in mouse colonies are colony management and animal house hygiene. Colony management includes systems of mating and weaning, aggregation of young mice into larger or smaller cages, crowding and cage size and construction, movement of stock between rooms, influx of mice from outside sources and removal of other mice, adequacy of diets and the use of supplements, deployment of staff and interchange of staff duties, etc. Under the heading of animal house cleaning the following topics are dealt with: cage and rack cleaning, cleaning and refilling of water bottles, handling of food from storage to dispensing in individual cages, disposal of waste food and bedding, employment of some recording system and the practice of post-mortem examinations. (15 references)

123. U. S. DEPARTMENT OF AGRICULTURE. *Animal Diseases. The Yearbook of Agriculture*. Washington, D. C., Gov. Printing Office, 1956, 591 pp.

The articles contained in this book are arranged under the following main headings: Prevention and treatment of diseases; diseases and parasites affecting cattle, swine, sheep, goats, poultry, dogs, cats, horses, mules, fur-bearing animals.

124. WEIPERS, W. L. Control of infection in laboratory cats and dogs. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 4: 21–8, 1956.

The maintenance of healthy dog and cat colonies and the control of laboratory infections are discussed. Essential points are: selection of the correct type of animal, isolation of premises, immunization against disease, housing, personnel and provision for veterinary consultation. The main infectious diseases affecting laboratory dogs and cats are: distemper, contagious canine hepatitis, leptospirosis, infectious laryngitis, skin infections or ectoparasites in dogs and feline enteritis, influenza or infectious pneumonitis in cats.

125. WHITTEN, W. K. The effect of removal of the olfactory bulbs on the gonads of mice. *J. Endocrinol.* 14: 160–3 (Oct.), 1956.

The ovaries and uteri of mature female mice rendered anosmic by removal of the olfactory bulbs were significantly smaller than those of control animals. Corpora lutea were absent or atrophic, and the vagina was closed in most of these animals. No effect on the testes of anosmic males was observed. The accessory glands were lighter and contained less secretion, but the epithelium appeared unchanged. Body weights of both male and female mice were reduced. (Author's summary)

126. ANDREW, W. AND PRUETT, D. Senile changes in the kidney of Wistar Institute rats. *Am. J. Anat.* 100: 51–79 (Jan.), 1957.

The kidneys of 50 Wistar Institute rats, including young (75–100 days) "middle-aged" (300 days) and senile (868–1170 days) have been studied. The histological aspect of the kidney in senile rats was found to be considerably different from that in young and "middle-aged" animals. (Condensed from author's summary)

127. AWAD, F. I. The intradermal sarcocystin test. *Am. J. Vet. Research* 18: 703–4 (July), 1957.

The possibility of applying the skin test in the diagnosis of sarcosporidiosis is studied in guinea pigs and rabbits infected artificially with *Sarcocystis tenella* or *leporum*. Since positive reactions to the skin test often occur in the absence of established infection, the test has little specific diagnostic value but can be used as a screening test.

128. BAKER, J. A. Development and expectations of the new vaccines. Paper presented at 7th Gaines Vet. Symposium, Kankakee, Ill., Oct. 23, 1957, pp. 15–9.

A dual vaccine consisting of egg-cultivated canine distemper (CD) virus and tissue-cultured infectious canine hepatitis (ICH) virus was tested in dogs for safety and effectiveness and minimal immunizing dose. The vaccine proved safe and effective if 250 or more egg-measured doses of CD virus and 63 or more of tissue-cultured ICH virus was given subcutaneously to dogs 9 wk. of age or older. Studies on puppies of various ages from immune and nonimmune dogs revealed that puppies with maternal protection could not be immunized, while those without maternal protection could be, even at 1 wk. of age. Maternal antibodies were found to transfer in utero in an amount approximately 3% of the mother's serum titer, and after intake of colostrum puppies' titers were 77% of the mother's serum titer. The serum titers acquired by puppies disappeared gradually, with higher titers persisting longer than lower ones. On the basis of the mother's serum titer, therefore, it became possible to predict the age at which maternal protection would disappear, the puppies would become susceptible and they could be immunized. A nomograph was designed which permits, on the basis of a mother's titer, a prediction of the age at which her puppies could be immunized while yet unborn and thereby make

possible maximum protection from vaccines by vaccination at the earliest possible age. (Author's summary)

129. BARKE, A. AND GIERSCHIK, H. Piperazin als Wurmmittel für Tiere. (Piperazine as an anthelmintic for animals.) *Deut. tierärztl. Wochschr.* 64: 177–80 (Apr.), 1957.

Mice injected i.p. with a 10% solution of piperazine citrate tolerated doses of 2 gm/kg without showing signs of toxicity but died within 10 min. after 4 gm/kg. Two cats were given by stomach tube 440 and 530 mg/kg, respectively, dissolved in sugar water; the smaller dose caused no toxic effects while the larger one produced vomiting. A 3rd cat tolerated a dose of 675 mg/kg piperazine adipate without vomiting. Two dogs, 33 and 42 kg, were given by stomach tube 33 and 42 gm/kg, respectively, of piperazine adipate. The larger dog vomited after 45 min. while the smaller one showed no untoward reaction.

130. BEVERLEY, J. K. A. Toxoplasmosis. *Vet. Record* 69: 337–42 (Mar. 16), 1957.

Infections by *Toxoplasma gondii* in dogs, cats, rats, rabbits, hares and birds are reviewed.

131. BEVERLEY, J. K. A. AND FRY, B. A. The treatment of experimental toxoplasmosis in rabbits. *Brit. J. Pharmacol.* 12: 185–8 (June), 1957.

The efficiency of sulfadimidine in experimental toxoplasmosis was compared with that of pyrimethamine and dapsone. The manner in which the therapeutic effect is influenced by the ability of individual rabbits to acetylate sulfonamides was studied.

132. BICKS, V. A. Infection of laboratory mice with *Corynebacterium murium*. *Australian J. Sci.* 20: 20–1 (July), 1957.

During routine examinations of experimental mice occasional animals showed caseous lesions in the liver or lungs, often accompanied by severe inflammation in the colon. The cultured organisms showed biochemical reactions agreeing with those recorded for *C. murium*. Intravenous and intraperitoneal inoculation of a suspension of the organism into experimental mice regularly produced infection and death in 4 and 7–14 days, respectively. Inconclusive results were obtained by introduction of the organism by nasal and oral routes.

133. BILD, C. E. Fluid therapy in the dog. *J. Am. Vet. Med. Assoc.* 131: 97–101 (July 15), 1957.

For the young pup or kitten that needs water and electrolytes, plain lactated Ringer's solution or Polysal or Ionosal D-CM (10–15 cc/lb) is indicated and given subcutaneously. There are no contraindications for using solutions intravenously except that in the very small animal it is often impractical. For resuscitative aid of surgical patients, these solutions should be used i.v., with 5% dextrose and with the additives.

134. BLANK, F. Favus of mice. *Can. J. Microbiol.* 3: 885–96 (Oct.), 1957.

Isolated cases and family epidemics of mouse favus were found in the lower St. Lawrence Valley, especially in the Kamouraska County. The specific agent of mouse favus was repeatedly isolated from animals (mice, cats, dogs, fox) and children and adults (smooth skin and scalp). The mouse is the normal host of the dermatophyte. Cats and dogs acquire the disease from mice and transmit it to man. The author suggests that the specific agent of favus of mice should be named *Microsporum quinckeanum*. (Condensed from author's abstract)

135. BLOUNT, W. P. *Rabbits' Ailments. A Short Treatise on the Domestic Rabbit in Health and Disease.* 2nd ed. Idle, Bradford, England, "Fur and Feather," 1957, 192 pp.

The book contains the following chapters: the rabbit in health; introduction to disease; specific diseases of rabbits (bacterial, viral, external and internal parasites, fungal infections, poisons, rickets); nonspecific diseases (digestive, cardiovascular, urinary, reproductive system); sanitation and nutrition.

136. BOCH, J. Versuche zur Behandlung der Kaninchenkokzidiose mit Nitrofurazon (Furacin-W). (Treatment of coccidiosis in rabbits with nitrofurazone.) *Berlin u. Münch. tierärztl. Wochschr.* 70: 264–7, 1957.

The effect of "Furacin-W" was studied in 48 rabbits experimentally infected with coccidiosis. Oral administration of 0.5–1.0 gm/kg body weight had a prophylactic effect while doses of 1.5–2 gm/kg decreased losses in already infected animals.

137. BUXTON, A. *Salmonellosis in Animals.* Farnham Royal, Buckshire, England, Commonwealth Agricultural Bureaux (*Review Series* No. 5), 1957.

Contains the following chapters: General characteristics of *Salmonella*; classification of *Salmonella*; distribution of *Salmonella* serotypes among animals (horses, mules, cattle, sheep, goats, pigs, dogs, cats, poultry, fur-bearing animals, rodents, reptiles, insects, ticks); symptoms and lesion of *Salmonella* infections in animals; epidemiology of *Salmonella* infections in animals; immunology of *Salmonella* infections in animals; antibacterial substances; public health aspects of *Salmonella* infections in animals.

138. CATHIE, I. A. B. II. An appraisal of the diagnostic value of the serological tests for toxoplasmosis. *Trans. Roy. Soc. Trop. Med. Hyg.* 51: 104–10 (Mar.), 1957.

The dye test and the complement-fixation test are discussed and their reliability for the diagnosis of toxoplasmosis is confirmed.

139. CHAI, C. K. Leukopenia: an inherited character in mice. *Science* 126: 125 (July 19), 1957.

The mouse stocks used were the large and small strains and their hybrid generation of the F_1, F_2, 1st, 2nd and 3rd backcrosses. The small mice were produced in the 17th–20th generation of inbreeding, the large mice in the 3rd–8th generation. Leukopenia in the small mice was found to be an inherited character, possibly determined by a small number of genetic factors.

140. CHUTE, H. L. AND O'MEARA, D. C. A bibliography of avian mycosis (partially annotated). *Maine Agr. Expt. Sta. Misc. Publ.* No. 631, Oct., 1957, 81 pp.

521 references, some with annotations, are listed.

141. CLARK, C. H. AND WALLACE, C. R. Canine electrocardiography. *Auburn Vet.* 14: 17–54, 1957.

A detailed account of the technique of electrocardiography in the dog and the interpretation of the results is given. The normal EKG and heartbeat are presented, and notes on the diagnosis and treatment of heart diseases are included.

142. COFFIN, D. L. Fluorescent antibody technique in veterinary research. *J. Am. Vet. Med. Assoc.* 130: 438–40 (May 15), 1957.

The use of fluorescein-labeled antibody as a histochemical technique to detect an antigenic agent is a practical, specific research tool. In the veterinary field, it has been employed to study in-

fectious hepatitis of dogs and canine distemper. It undoubtedly will prove useful in many other phases of veterinary research and for disease diagnosis. (Condensed from author's summary)

143. COLEMAN, R. M. AND Von BRAND, T. Blood pyruvate levels of rats during hemoprotozoan infections. *J. Parasitol.* 43: 263–70 (June), 1957.

Blood pyruvate levels were determined in uninfected white rats and in white rats infected with *Trypanosoma cruzi*, *T. congolense*, *T. equiperdum*, *T. gambiense* and *Plasmodium berghei*. The degree of parasitemia was expressed as number of trypanosomes/ml of blood.

144. CORBIN, J. E., SCHAEFER, H. C. AND VANDEPOPULIERE, J. M. Recent findings in nutritional deficiencies in laboratory animals. *Proc. Animal Care Panel* 7: 175–92 (Sept.), 1957.

Dietary requirements and deficiency symptoms are discussed for minerals (Ca, P, NaCl, I, Fe, Cu, Co, Zn, Mn, F, Mg, K, S, Mo), proteins (amino acids) and vitamins (A, C, D, E, B_1, B_2, B_6, B_{12}, K), nicotinic, pantothenic, para-amino benzoic, folic acids, biotin, choline, inositol).

145. CORNELIUS, C. E. New concepts and methods in the laboratory diagnosis of canine liver disease. Paper presented at 7th Gaines Vet. Symposium, Kankakee, Ill., Oct. 23, 1957, pp. 20–4.

Indications for and the classification of liver function tests in the dog are presented. Procedures for the determination of serum bilirubin, urinary azo-pigment glucuronide and urobilinogen, alkaline phosphatase, serum protein, prothrombin and coagulation time, serum cholesterol, blood uric acid, serum glutamic transaminase and the Bromsulphalein dye test are discussed and normal values are given. Results from liver function tests in canine icterus and liver disease are tabulated.

146. COTCHIN, E. Neoplasia in the cat. *Vet. Record* 69: 425–34 (Apr. 13), 1957.

After giving a definition of neoplasm the author presents the incidence of tumors in cats with regard to age and sex and the system of origin, that is: alimentary, cutaneous, genital, lymphatic, skeletal, urinary, respiratory, endocrine and eye. The data are based on 464 tumors, of which 328 were malignant, with known origin.

147. COVER, M. S. A review of the chemotherapy of avian viral and bacterial infections. *J. Am. Vet. Med. Assoc.* 131: 465–9 (Nov. 15), 1957.

A review is presented on chemotherapy of viral diseases such as psittacosis, and the following bacterial diseases: infectious coryza, fowl cholera, pullorum disease, fowl typhoid, erysipelas, bluecomb disease, chronic respiratory disease complex and infectious synovitis. (30 references)

148. CRAIG, J M. AND SCHWARTZ, R. Histochemical study of the kidney of rats fed diets deficient in potassium. *Arch. Pathol.* 64: 245–54 (Dec.), 1957.

Sprague-Dawley rats fed diets deficient in Na and K ate poorly and their growth ceased shortly after being given the diet. They became polyuric within 4 days. Both K- and Na-deficient diets caused histological alterations in all zones of the renal tubule and lymphocytic infiltration of the renal cortex. The solely Na-deficient group had only slight disturbances in the mitochondrial pattern. K-deficient rats given $NaHCO_3$ demonstrated heart lesions which did not occur when $NaHCO_3$ was substituted by NaCl.

149. DAVIES, M. E. The value of routine testing for pancreatic enzyme (trypsin) deficiency in canine faeces. *Vet. Record* 69: 1071 (Nov. 16), 1957.

The trypsin test used routinely in a diagnostic laboratory for the examination of feces from dogs suffering from various enteric disturbances (nonspecific diarrhea) is described. The titer of free trypsin in feces from healthy dogs varied from 1:20 to 1:2,000. Positive cases showed either no free trypsin or titers of 1:10 or 1:20. Follow-up of progress of positive cases revealed that marked improvement was produced in a number of dogs by administration of pancreatic extract; other dogs responded to warming, antibiotics or change of diet.

150. DETWEILER, D. K. Electrocardiographic and clinical features of spontaneous auricular fibrillation and flutter (tachycardia) in dogs. Comparison with spontaneous auricular fibrillation and flutter in other species and with experimentally induced arrhythmias in dogs. *Zentr. Veterinärmed.* 4: 509–56, 1957.

Twenty-two cases of spontaneous auricular fibrillation, 2 cases of spontaneous auricular flutter, and 2 cases of auricular flutter induced during the treatment of auricular fibrillation with quinidine are reported in dogs. Clinical and post-mortem findings are described. (From author's summary)

151. ERICKSON, B. R., SMITH, D. L. AND D'AMOUR, F. E. Effect of environmental temperature in traumatic shock. *Proc. Soc. Exptl. Biol. Med.* 94: 1–4 (Jan.), 1957.

The effect of 9 environmental temperatures between 10° and 40°C on survival time and on body temperature of rats in traumatic shock was studied. The results indicate: that the optimum temperature is 20°. Survival time at this temperature is significantly better than at 17.5° or 25°; lower or higher temperatures are increasingly harmful. Animals in shock appear to be poikilothermic, their body temperatures tending to approach the environmental temperature. (Author's summary)

152. EYLES, D. E. AND COLEMAN, N. An evaluation of the effect of sulfones on experimental toxoplasmosis in the mouse. *Antibiotics & Chemotherapy* 7: 577–85 (Nov.), 1957.

Experiments with white mice of the NIH general purpose strain indicated that sulfones are less effective in treating Toxoplasma gondii than are sulfonamides. Sulfones are of value only in cases where sulfonamides are not tolerated. Pyrimethamine and 4,4′-diaminodiphenyl sulfone had a synergistic effect.

153. EYSSEN, H., DE SOMER, P. AND VAN DIJCK, P. Further studies on antibiotic toxicity in guinea pigs. *Antibiotics & Chemotherapy* 7: 55–64 (Feb.), 1957.

The following antibiotics were administered orally to guinea pigs in 1-ml solution or suspension: penicillin, bacitracin, chlortetracycline, streptomycin and chloramphenicol. The last one did not cause mortality, while the other antibiotics produced the same syndrome of intoxication by acting on the intestinal flora. Phenomena of resistance to antibiotics are discussed.

154. FARHI, A. Contribution à l'étude de l'action des antibiotiques sur l'immunité. Action des antibiotiques dans les infections experimentales de la souris. Cas d'une vaccination anteriéure à l'infection; cas d'une vaccination associée à l'infection. (Action of antibiotics on immunity. Action of antibiotics in experimental infec-

XUM

tions of mice. Effect of vaccination before infection; effect of vaccination at the time of infection.) *Compt. rend.* 244: 2201–3 (Apr. 15); 2262–3 (Apr. 24), 1957.

Mice, infected with *Salmonella typhimurium* or *Diplococcus pneumoniae*, but not previously vaccinated, survived after treatment with antibiotics but succumbed readily to reinfection. Vaccinated animals resisted reinfection even with a dose 10 times as large as that administered to nonvaccinated mice.

155. Feldman, W. H., Karlson, A. G. and Herrick, J. F. *Mycobacterium ulcerans*. Pathogenesis of infection in mice, including determinations of dermal temperatures. *Am. J. Pathol.* 33: 1163–79 (Nov.–Dec.), 1957.

White mice, strain C, were inoculated intravenously, subcutaneously or intracerebrally with *Mycobacterium ulcerans*. The pathogenesis of *Myco. ulcerans* was dependent to a considerable extent on the temperature of the area where the bacteria were introduced or eventually found lodgment. For comparison, the temperature of the tail of normal mice was determined by means of thermistor-thermometers; it was about 11°–12°C lower than the temperatures recorded for the rectum and approximated that of the external environment.

156. Flamm, H. Klebsiella-Enzootie in einer Mäusezucht. (*Klebsiella*-endemic in a mouse-breeding establishment.) *Schweiz. Z. allgem. Pathol. u. Bakteriol.* 20: 23–7, 1957.

A disease of white mice, manifesting itself by the sudden appearance of throat abscesses accompanied by adenitis of the supraclavicular glands is reported. Other organs may be involved. The disease, which is due to an infection with *Klebsiella pneumoniae*, may result from a slight injury during mastication. An identical syndrome could be produced by experimental inoculation with *Klebsiella* under the buccal mucous membrane.

157. Fontaine, M. Le diagnostic de la maladie de Rubarth par sero-précipitation. (Diagnosis of canine virus hepatis by a precipitation test.) *Rev. pathol. gén. comparée* 57: 941–6, 1957.

Contagious hepatitis was diagnosed by Larin's quantitative flocculation method. More reliable results were obtained by Oudin and Ouchterlony's technique, using precipitation in agar medium. (Author's summary)

158. Fremming, B. D., Harris, M. D., Jr., Young, R. J. and Benson, R. E. Preliminary investigation into the life cycle of the monkey lung mite (*Pneumonyssus foxi*). *Am. J. Vet. Research* 18: 427–8 (Apr.), 1957.

Experiments with *Macaca mulatta* showed that transplacental transfer is unlikely to occur in the life cycle of *Pneumonyssus foxi*. *M. mulatta* monkeys free of lung mites were raised in special sterile environments.

159. Frenkel, J. K. and Hitchings, G. H. Relative reversal by vitamins (*p*-aminobenzoic, folic, and folinic acids) of the effects of sulfadiazine and pyrimethamine on *Toxoplasma*, mouse and man. *Antibiotics & Chemotherapy* 7: 630–8 (Dec.), 1957.

The RH strain of *Toxoplasma* was maintained by i.p. passage twice weekly in white Swiss mice (Hauschka strain). Treatment was administered by feeding the following drugs in Purina chow: mg % of feed, sulfadiazine 60, pyrimethamine 30 and 100, sulfadiazine 30 plus pyrimethamine 30. The untreated infection was uniformly fatal and vitamin treatment neither accelerated nor delayed the death. Sulfadiazine alone and the low dosage of pyrimethamine caused survival of most of the mice and development of immunity in about 50%. The large dose of pyrimethamine produced survival of all and immunity in most mice. The combination of the 2 drugs effected cure in all mice. The efficiency of each single drug was impaired by addition of *p*-aminobenzoic or folic acid but not by folinic acid or dried brewer's yeast. But both folinic acid and yeast improved the therapeutic index of the drug combination.

160. Gabka, J. Tierexperimenteller Beitrag zur Frage der Entstehung primärer Missbildungen durch die Toxoplasmose. (Animal experiments on the causation of primary malformations by toxoplasmosis.) *Zentr. allgem. Pathol. u. pathol. Anat.* 96: 135–46, 1957.

Toxoplasmosis infection was induced in groups of mice and rats and its effect on the 2nd generation of animals was studied. The tests with mice were not sufficiently conclusive since not enough mice responded to the infection. The experiments with rats showed that toxoplasmosis infection in the mother animal may cause death and facial clefts in the fetus and the young.

161. Garciá Rodríguez, I. and Herrera Repullo, A. Una nueva enfermedad infectocontagiosa del conejo y un nuevo germen patógeno. (A new infectious disease of rabbits—pseudotularemia caused by *Past. pseudotularensis* n. sp.) *Bol. Cons. Col. vet. Esp.* 1: 29–38, 1957.

The disease occurred in a rabbitry comprising 350 rabbits of which 80% were affected, the younger ones being less susceptible. Mortality was 100%. The main symptoms were salivation, nasal discharge, dyspnea, and difficulty in locomotion; the course of the disease was 4–6 days. Post-mortem findings included serofibrinous exudate (slightly hemorrhagic at times) in the pleural, pericardial, and peritoneal cavities, false membrane on the visceral pleura, petechiae and hepatization in the lungs and small foci of necrosis in the lungs, heart, kidneys and liver and, in some cases, abscesses (containing a thick whitish pus) on the inner aspect of the jaw and at the base of the neck. An organism was isolated from the blood, exudates and lesions. It was pathogenic for laboratory animals and reproduced the disease in rabbits and white rats. By its morphological, staining and cultural characteristics it was identified as a *Pasteurella*, closely similar to *Past. tularensis* but differing from it in motility, fermentation reactions, growth on egg or cystine, and in its pathogenicity for guinea pigs. The name *Past. pseudotularensis* n. sp. is suggested for the organism and pseudotularemia for the disease. (*Vet. Bull.* 28: Abstr. No. 2027, 1958)

162. Garner, R. J. *Veterinary Toxicology*. London, Bailliere, 1957, 415 pp.

The action of inorganic and organic compounds, poisonous plants and radioactive materials on various animals is discussed. Animals referred to are rat, mouse, guinea pig, rabbit, horse, cow, sheep, goat, pig, dog, cat, fowl, etc. A bibliography follows each chapter.

163. Georg, L. K., Roberts, C. S., Menges, R. W. and Kaplan, W. *Trichophyton mentagrophytes* infections in dogs and cats. *J. Am. Vet. Med. Assoc.* 130: 427–32 (May 15), 1957.

A survey of ringworm in animals, conducted by the mycology unit of the Communicable Disease Center, has indicated that *Trichophyton mentagrophytes* is a fairly common cause of ringworm in dogs and an occasional cause of infections in cats. It also produces ringworm in other domesticated as well as wild animals, and is commonly isolated from the hair of rodents with or without signs of infection. Eighteen *Trichophyton mentagrophytes* infections in

dogs and 2 in cats have been described. (Condensed from author's summary)

164. GLEDHILL, A. W. AND NIVEN, J. S. F. The toxicity of some bacterial filtrates for mice pre-infected with *Eperythrozöon coccoides*. *Brit. J. Exptl. Pathol.* 38: 284–90 (June), 1957.

A method to infect mice with *Eperythrozöon coccoides* is described.

165. HABERMANN, R. T. AND WILLIAMS, F. P., JR. Diseases seen at necropsy of 708 *Macaca mulatta* (rhesus monkey) and *Macaca philippinensis* (cynomolgus monkey). *Am. J. Vet. Research* 18: 419–26 (Apr.), 1957.

The gross and microscopic findings and the percentage occurrence of diseases among necropsies performed on 615 rhesus and 93 cynomolgus monkeys are presented. (Condensed from author's summary)

166. HABERMANN, R. T. AND WILLIAMS, F. P., JR. The efficacy of some piperazine compounds and stylomycin in drinking water for the removal of oxyurids from mice and rats and a method of critical testing of anthelmintics. *Proc. Animal Care Panel* 7: 89–94 (June), 1957.

Piperazine adipate and piperazine citrate and tartrate in the drinking water removed 99.1% and 84.6%, respectively, of oxyurids from NIH strain mice and 86.7% and 89.8%, respectively, from Sprague-Dawley rats. Piperazine dihydrochloride was 96.5% effective in eliminating pinworms from mice; stylomycin in the drinking water removed 99.5% of the pinworms from mice and 100% from rats. None of the above drugs were effective for removal of tapeworms. Techniques of exposure, collecting and counting of worms and of treating the animals are indicated.

167. HEWITT, H. B. A sensitive method for the assay of androgens based on their power to alter the reactions of the mouse kidney to chloroform. *J. Endocrinol.* 14: 394–9 (Jan.), 1957.

High susceptibility to small concentrations of chloroform vapor, leading to necrosis of the renal tubules, was noted in mature male mice while castrated males and normal females were entirely unsusceptible. Full susceptibility could be restored in the castrated mice by administration of androgens. This phenomenon may be used as a means of assaying androgens.

168. HUME, E. M. Monkey welfare. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 5: 61–8, 1957.

Monkeys in captivity are highly susceptible to rickets but can be cured by exposure to ultraviolet rays of a Hg-vapor quartz lamp. Marmosets thus treated could be bred in captivity, but since the ultraviolet light probably overstimulated the pituitary gland, no 2nd generation could be reared. Rickets and osteomalacia could also be prevented by supplying vitamin D from another source than artificial light, such as exposure to sun through Vitaglass or oral administration of calciferol. A complete diet as well as environmental temperatures not lower than 70°F are other factors essential for the welfare of captive monkeys.

169. INNES, J. R. M. AND O'STEEN, W. K. Splayleg in rabbits. An inherited disease analogous to joint dysplasia in children and dogs. *Lab. Invest.* 6: 171–86 (Mar.–Apr.), 1957.

A condition, commonly called "splayleg," in rabbits born from normal parents, has been defined. Affected and normal animals occur in a litter in a ratio of about 3:1. The disease is first recognizable when the rabbits normally start to walk. There may be complete immobilization due to a malalignment of one, or both, hip joints, sometimes plus one or both shoulder joints. Postural contractures of the limbs develop later and the animals may be stunted in growth but can be kept alive with care. The disease is inherited, but the cause is unknown. The condition is regarded as a variant of achondroplasia (chondrodystrophia fetalis), restricted in its pathologic effects to the hip and shoulder, which in its severe lethal form has occurred in rabbits, as well as in calves, dogs, and man. (Condensed from author's summary)

170. ITO, S., IMAIZUMI, K., TAJIMA, Y., ENDO, M. AND KOYAMA, R. A disease of rats caused by a pleuropneumonia-like organism (PPLO). *Japan. J. Exptl. Med.* 27: 243–8, 1957.

A polyarthritis of rats was characterized by redness, swelling, suppuration, necrosis and sometimes natural amputation of the limbs or more often the digits. An organism identical with L4 of the pleuropneumonia group was shown to be the causal agent. (*Vet. Bull.* 28: 1397, 1958)

171. JACOBS, L. AND LUNDE, M. N. A hemagglutination test for toxoplasmosis. *J. Parasitol.* 43: 308–14 (June), 1957.

The hemagglutination technique is based on the phenomenon that red blood cells exposed to an antigen become sensitized to homologous antibody. The test was performed by adding 0.05 ml of sensitized red cells to 0.5 ml of each test serum dilution (the test serum was diluted in 1:50 normal rabbit serum). Antigens were prepared from peritoneal exudates of mice. A macroscopic system of grading the hemagglutination reaction was devised. The test offers promise of providing a practical serological procedure for the diagnosis of toxoplasmosis.

172. JONES, L. M. *Veterinary Pharmacology and Therapeutics*. 2nd ed. Ames, Iowa State University Press, 1957, 944 pp.

The various drugs are considered with regard to their basic pharmacology and their clinical application. The effects of drugs acting on the skin and mucous membranes, digestive tract, central nervous and autonomic nervous system, blood and heart, reproductive system, and tissue metabolism, as well as anesthetics, chemotherapy and drugs with lethal effect are discussed. Appendix 1 deals with use and dosage of selected drugs, appendix 2 with seldom used or obsolete drugs.

173. KAPLAN, H. M. Septicemic, cutaneous ulcerative disease of turtles. *Proc. Animal Care Panel* 7: 273–7 (Dec.), 1957.

A septicemic, cutaneous ulcer disease has been found in turtles and does not appear to have been described elsewhere. The coliform bacterium, *E. freundii*, is apparently the etiologic agent. This is a soil and water bacterium that may also live harmlessly in the intestine. The possibility of its being pathogenic to many diverse hosts is not to be overlooked, and the turtle might act as a reservoir. Transmission of turtle disease into mammals has hitherto seemed unlikely in the established opinions in the literature. (Author's summary)

174. KENT, S. P., VAWTER, G. F., DOWBEN, R. M. AND BENSON, R. E. Hypervitaminosis D in *Macaca mulatta* monkeys. A clinical and pathologic study. *U. S. Air Force, School of Aviation Medicine Rept.* 57–145, Sept., 1957.

Accidental acute vitamin D intoxication developed in a colony of 558 monkeys (*Macaca mulatta*) because of an error in the manu-

XUM

facture of the monkey food whereby the entire group received excessive amounts of Ca, P and vitamin D for almost 3 mo. A number of deaths occurred before the diagnosis was established. The clinical and pathological observations while the colony was on the toxic diet and for 1 yr. thereafter are reported.

175. KRISE, G. M. AND WALD, N. Effects of repeated experimental blood loss on the hematology of the *Macaca mulatta* monkey. *U. S. Air Force School of Aviation Medicine Rept.* 57–149, Sept. 1957, 6 pp.

The effects of weekly bleedings of 18% and 24% blood volume in *Macaca mulatta* monkeys on red and white blood cells, hemoglobin, hematocrit, reticulocytes, leukocytes and lymphocytes were determined. The results indicated that the recovery rate of the marrow could not keep pace with the rate of loss.

176. LAINSON, R. The demonstration of *Toxoplasma* in animals, with particular reference to members of the Mustelidae. *Trans. Roy. Soc. Trop. Med. Hyg.* 51: 111–7 (Mar.), 1957.

The isolation of *Toxoplasma* constitutes the only real proof of infection. Since the organism cannot be cultivated on media free from living cells, the incidence of the disease among animals was investigated in order to find a suitable laboratory animal for inoculation of *Toxoplasma*. Spontaneous infections occur in domestic and laboratory rabbits and guinea pigs. Dogs, cats and other carnivores may become infected after ingesting infected, or raw, rabbit flesh. Rats are generally resistant to infection. While the mouse had been considered to be the experimental animal of choice for the isolation of the parasite, the multimammate rat (*Mastomys coucha*) was found to be more highly susceptible to *Toxoplasma* isolated from rabbits and some mustelid animals than the laboratory mouse. It is suggested that the multimammate rat might prove more suitable in studies on this parasite. Brain tissue of the host was found to be the best material for passage into mice, the intraperitoneal route is to be preferred, and subinoculations should be carried out at weekly intervals to detect avirulent strains of *Toxoplasma*.

177. LEVINE, N. D. Protozoan diseases of laboratory animals. *Proc. Animal Care Panel* 7: 98–126 (June), 1957.

A review of the following protozoan diseases of laboratory animals (rat, mouse, rabbit, guinea pig, hamster, dog, cat, chicken, pigeon) and their diagnosis and treatment is presented: trichomoniasis, giardiasis, amoebiasis, coccidiosis, toxoplasmosis and balantidiasis. Numerous references are listed.

178. MAYER, K., LACROIX, J. V. AND HOSKINS, H. P., ed. *Canine Surgery. A Text and Reference Work.* 4th ed., Evanston, Ill., Am. Veterinary, 1957, 820 pp.

The material is distributed into the following chapters: Anatomy; physiology; healing and repair; surgical principles; sterile technic; sutures and ligatures; approach and restraint; anesthesia; presurgical care; wound protection; physiological consideration of some postoperative conditions; the skin; dental surgery; the mouth; tonsils; larynx and trachea; sublingual and submaxillary salivary cyst; the nose; ears; eyes and eyelids; thyroid gland; neck; thorax; abdomen; genitourinary system; mammary glands; anus and rectum; legs; fractures; luxations; cosmetic surgery.

179. MILLEN, J. W. AND DICKSON, A. D. The effect of vitamin A upon the cerebrospinal-fluid pressures of young rabbits suffering from hydrocephalus due to maternal hypovitaminosis A. *Brit. J. Nutrition* 2: 440–6, 1957.

The relationship of hypovitaminosis A and increased intracranial pressure is discussed. A method for measuring intraventricular pressure and the application of ventriculography in hydrocephalic rabbits is described.

180. MOORE, B. Observations pointing to the conjunctiva as the portal of entry in *Salmonella* infection of guinea-pigs. *J. Hyg.* 55: 414–33 (Sept.), 1957.

The techniques of goggling are described. In the improved technique each eye was goggled separately by using a "bunion pad" to which an elliptical patch of cleared x-ray film was attached with adhesive, thus raising the lenses some distance from the conjunctival surface.

181. NELSON, J. B. The etiology and control of chronic respiratory disease in the rat. *Proc. Animal Care Panel* 7: 30–40 (Mar.), 1957.

Chronic respiratory disease in rats comprises 2 separate entities: infectious catarrh caused by pleuropneumonia-like organisms, and enzootic bronchiectasis caused by a virus. They may occur independently or coexist in the same animal. Pleuropneumonia-like organisms tend to localize in the upper respiratory tract and the middle ears while the virus is principally located in the lungs. Both infections are transmissible by nasal instillation and contact in rats and mice. Both diseases can be controlled and rat colonies free of them can successfully be maintained.

182. RENOUX, G. AND SACQUET, E. Brucellose spontanée du lapin domestique. (Spontaneous brucellosis in domestic rabbits.) *Arch. inst. Pasteur Tunis* 34: 231–2, 1957.

Brucella intermedia was isolated from the liver and spleen of 2 rabbits out of a group of 98 which had been purchased in Tunisia. No microscopically detectable lesions were noted. *Brucella* agglutinins were found in the sera of 25 of the batch. Spontaneous brucellosis may not be infrequent in rabbits.

183. SCHIRMER, R. G. Cerebrospinal fluid analysis and its significance in diagnosis. Paper presented at 7th Gaines Vet. Symposium, Kankakee, Ill., Oct. 23, 1957, pp. 12–14.

The technique of cisternal puncture for withdrawal of cerebrospinal fluid in the dog is described and the diagnostic value of an examination of the cerebrospinal fluid in certain diseases of the central nervous system is pointed out. Data of normal cerebrospinal fluid pressure and physical and cytological characteristics are reported.

184. SEMELLINI, L. Controllo chemioterapico della coccidiosi epatica ed intestinale del coniglio nei piccoli allevamenti a carattere familiare. (Chemotherapy of hepatic and intestinal coccidiosis in rabbits.) *Nuova Vet.* 33: 273–80, 1957.

The various clinical forms of coccidiosis and the treatment of the hepatic and intestinal forms in 25 outbreaks of which 11 (222 animals) were of the intestinal, 6 (160 animals) of the hepatic and 8 (210 animals) of the mixed type were described. The intestinal form was treated with sulfaquinoxaline sodium 0.0344% in the drinking water, and for the hepatic and mixed forms 0.3 gm/kg of hexachloroethane was added to the food once on the 15th and once more on the 31st day of such treatment. Treatment was uniformly successful (clinical cure). All the animals including their progeny, however, remained carriers of coccidia thus providing evidence of a state of premunition arising after treatment. (*Vet. Bull.* 28: Abstr. No. 3200, 1958)

185. SMITH, H. A. AND JONES, T. C. *Veterinary Pathology.* Philadelphia, Lea, 1957, 959 pp.

The signs, gross and microscopic lesions and in most cases the diagnosis of the disorders and diseases of domestic animals, including the cat and dog, are treated under the following chapter headings: Cellular degenerations; mineral deposits, pigments; disturbances of growth and circulation; inflammation and body reactions; neoplasia; causes and nature of disease; diseases caused by viruses and rickettsiae, simple and higher bacteria, fungi and spirochetes, protozoa, parasitic helminths and arthropods, extraneous poisons and disorders of metabolism; ionizing radiations; skin and appendages; musculoskeletal, respiratory, cardiovascular, hemic, lymphatic, digestive, urinary, genital, endocrine and nervous systems, organs of special senses.

186. STALKER, A. L. AND MCLEAN, D. L. The incidence of oedema in young guinea pigs. *J. Animal Technicians Assoc.* 8: 18–20 (June), 1957.

A disease of young guinea pigs characterized by liver damage and edema is described. The disease had been reproduced in 4 separate feeding experiments by a suspected batch of pelleted diet No. 18. The etiology of the disease has been investigated, so far without success. Contamination of grass by soil containing residual insecticide or weed killer is suggested as a possibility but further investigation is necessary. (Author's summary)

187. SULKIN, S. E., KRUTZSCH, P. H., WALLIS, C. AND ALLEN, R. Role of brown fat in pathogenesis of rabies in insectivorous bats. (*Tadarida b. mexicana*). *Proc. Soc. Exptl. Biol. Med.* 96: 461–4 (Nov.), 1957.

Studies on the progression of peripherally inoculated rabies virus in Mexican free-tailed bats (*Tadarida b. mexicana*) suggest that the brown (hibernating) fat plays a significant role in the pathogenesis of rabies in this animal. The studies in addition to including the rabies virus among those (polio virus and certain Coxsackie viruses) which exhibit lipotropism suggest that this may prove to be a characteristic feature of infection with "hardy" viruses. (Author's summary modified)

188. TEUSCHER, E. Eine neue praktische Flotationsmethode für den koprologischen Nachweis der Leberegeleier. (New flotation method for the identification of liver fluke eggs in feces.) *Schweiz. Arch. Tierheilk.* 99: 523–8, 1957.

Best results were obtained by adding to a suspension of feces a solution of 80 gm Zn sulfate and 25 gm sugar in 100 cc of water (sp. gr. 1.34) for the demonstration of *Fasciola hepatica* and *Dicrocoelium lanceolatum.*

189. VOGEL, H., WIDELOCK, D. AND FUERST, H. T. A microflocculation test for trichinosis. *J. Infectious Diseases* 100: 40–7 (Jan.–Feb.), 1957.

A new flocculation test is described for the serologic diagnosis of trichinosis. The antigen emulsion is easily prepared from materials of known concentration. The test is more specific although less sensitive than the complement fixation or the flocculation test by Bozicevich *et al.* Negative results are easily determined due to the greater homogeneity of negative reactions. Since serologic examinations may be negative shortly after onset of the disease, it is important to repeat such examinations periodically up to 9 wk. after the appearance of symptoms. (Author's summary)

190. WILLIAMS, F. P., JR. AND HABERMANN, R. T. An evaluation of the efficacy of stylomycin, phenothiazine, cadmium anthranilate, and the piperazine compounds for the removal of oxyurids in mice. *Am. J. Vet. Research* 18: 429–31 (Apr.), 1957.

The efficacies of 7 different anthelmintics for the removal of pinworms from mice were tested. Stylomycin was nontoxic and most effective (98.1%) in the administration of *Aspicularis tetraptera* from the cecum and *Syphacia obvelata* from the colon of mice. Phenothiazine removed 70.1% of the worms; parvex, pipcide, piperazine adipate, aminonucleoside of stylomycin and Cd anthranilate were less effective than stylomycin and phenothiazine. Stylomycin was not effective for removal of *Hymenolepsis* spp. from mice.

191. YOUNG, R. J. AND LUCAS, C. C. Choline deficiency in the guinea pig. *Can. J. Biochem. and Physiol.* 35: 1–6 (Jan.), 1957.

A dietary deficiency of choline in 4–6-day-old guinea pigs resulted in 100% mortality between the 3rd and 4th week. However, guinea pigs reared on an adequately supplemented purified diet for 3–4 wk. and then fed a choline-deficient diet for 6 wk. did not show any mortality. The livers of these animals showed a measurable increase in total liver fat at 6 wk.

192. ZUCKER, T. F. Pantothenate deficiency in rats. *Proc. Animal Care Panel* 7:193–202 (Sept.), 1957.

Pantothenate deficiency in the rat is associated with *1*) moderate growth inhibition; *2*) low coenzyme *A* content of tissues which leads to a reduction in ability to acetylate; *3*) excretion of porphyrins from the Harderian glands leading to "bloody whiskers;" *4*) graying of fur; *5*) tongue and mouth ulcer; *6*) hemorrhage and necrosis of the adrenal; *7*) activation of latent infection with *Corynebacterium kutscheri* in weanling rats, and *8*) duodenal ulcers in rats older than 15 wk. The latter 2 diseases were used to determine quantitatively that pantothenate-deficient rats bred for large body size showed a significantly greater incidence of these diseases than rats selectively bred for small body size. Genetics involved are discussed.

193. ALLEN, A. M. AND KINARD, R. F. Primary cutaneous inoculation tuberculosis in the *Macaca mulatta* monkey. *Am. J. Pathol.* 34: 337–47 (Mar.–Apr.), 1958.

Six juvenile *Macaca mulatta* monkeys were accidentally inoculated intradermally with tuberculous exudate which had contaminated the needles of a tattooing machine. Clinical and histological observations indicated that the lesions produced in the monkeys were those of primary cutaneous complex of tuberculosis. (From author's summary)

194. ANDERSEN, A. C. AND SULTZ, F. T. A developmental cataract in the dog. *Proc. Cong. Genet.* 10th Cong., Montreal, 1958.

Out of 1,129 purebred beagles observed 1 male showed complete bilateral cataract when 5 mo. of age. Matings with 5 normal dams produced 19 offspring with complete bilateral cataract, 2 with partial bilateral cataract, 1 nearly normal, and 3 normal. Puppies were killed for histological study between 41 and 60 days of age. Three defects were present: microphthalmia, retinal folding, and lens opacity. The cataract seemed to be a defect in the development of secondary lens fibers. Neither sex linkage nor an autosomal recessive was indicated. (*Vet. Bull.* 29: Abstr. No. 2214, 1959)

195. ANONYMOUS. A new serological service for dogs. *J. Am. Vet. Med. Assoc.* 133: 574–5 (Dec. 1), 1958.

The New York State Veterinary College at Cornell University, Dr. T. Benson, director, is giving a serological service for dogs which permits the use of a nomograph in distemper vaccination. In addition, other tests for immunity are available for distemper,

XUM

for infectious canine hepatitis and for 3 types of leptospiras (*L. canicola, L. icterohaemorrhagiae* and *L. pomona*).

196. ANONYMOUS. Atherosclerosis research. *Science* 127: 1107 (May 9), 1958.

The importation of baboons from Kenya by the Southwest Foundation for Research and Education (San Antonio) is announced. This animal is suitable for research on atherosclerosis since it is the only mammal other than man that is subject to the fatty deposits that characterize atherosclerosis.

197. ARMED FORCES INSTITUTE OF PATHOLOGY. A symposium on Some Infectious Diseases of Laboratory Rodents. *J. Natl. Cancer Inst.* 20: 861–1009 (May), 1958.

For abstracts see: Cook, J. E.; Griesemer, R. A.; Habermann, R. T.; Maurer, F. D.; Nelson, J. B.; Pappenheimer, A. M.; Saunders, L. Z.; Sokoloff, L.; Yost, D. H.

198. ARNALL, L. Experiences with cage-birds. *Vet. Record* 70: 120–8 (Feb. 8), 1958.

A survey of 463 cases of disease in 435 cage and other pet birds is presented. Diseases studied were injuries such as fractures, burns and scalds, tumors, dermoid cysts, abscesses, beak troubles, ectoparasites, feathering, skin, digestive, respiratory, nervous, reproductive disorders, and developmental abnormalities. Etiology, nature, diagnosis, treatment and outcome are discussed. The last chapter deals with general handling and sexing of cage birds.

199. AWAD, F. I. The complement-fixation test in the diagnosis of sarcosporidiosis. *Am. J. Vet. Research* 19: 1010–2 (Oct.), 1958.

The use of the complement fixation (CF) test as a method for diagnosing sarcosporidiosis in sheep is described. A frozen and thawed extract of the cysts yielded the most potent complement-fixing antigen. The test is specific in the diagnosis of sarcosporidiosis, and a titer of 1:10 is significant. While the test may sometimes fail, it is most useful in the diagnosis of active infections and can also be used to differentiate sarcosporidiosis from toxoplasmosis. (Author's summary modified)

200. BAKER, N., TUBIS, M. AND BLAHD, W. H. Metabolic and nutritional studies in mice with a hereditary myopathy (dystrophia muscularis). *Am. J. Physiol.* 193: 525–9 (June), 1958.

Nutritional, chemical and metabolic studies have been carried out on hereditarily muscular-dystrophic mice and their littermate controls. Certain characteristics of the dystrophic syndrome are described: denudation of the eyelids, periocular inflammation, tremors and an unusual reflex involving the head and neck, inflammation of the penis, and diminished bone growth. The dystrophic mice consumed, on the average, more food per day per unit body weight than their normal controls. Parenteral administration of vitamins A, D, E, the B-complex vitamins and ascorbic acid failed to reverse any of the dystrophic syndrome in 8 dystrophic mice. The metabolic rate was normal (per unit weight basis) as measured by the rate of CO_2 production; similarily, acetate-1-C^{14} was oxidized to $C^{14}O_2$ at the same rate in normal and dystrophic mice. Levels of plasma glucose, cholesterol, protein-bound I^{131}, and of liver cholesterol were not significantly different in a small group of normal and dystrophic mice. (Author's abstract)

201. BETHARD, W. F., WISSLER, R. W., THOMPSON, J. S., SCHROEDER, M. A. AND ROBSON, M. J. The effect of acute protein deprivation upon erythropoiesis in rats. *Blood* 13: 216–25 (Mar.), 1958.

Removal of protein from the diet was followed promptly by hemoconcentration, diminution in blood volume, and drastic reduction in erythropoiesis. These changes were reversible, after 35 days, upon addition of protein to the diet. Protein intake is more essential for maintenance of normal erythropoiesis than is total caloric intake. The data suggest that hemoglobin concentration within the vascular system is more important than red cell volume in regulating erythropoietic rate. (Condensed from author's summary)

202. BILD, C. E. Urine chloride determination in the dog. *J. Am. Vet. Med. Assoc.* 132: 256–7 (Mar.), 1958.

Urine chlorides were determined by using the Schribner revision of the Fantus test. The test requires 1 min. and costs 1 cent. The test is useful as a diagnostic aid.

203. BIMMER, E. AND MOHR, W. Therapie-Versuche bei experimenteller Mäuse-Toxoplasmose. (Therapy of experimental toxoplasmosis in mice.) *Z. Tropenmed. u. Parasitol.* 9: 225–34, 1958.

Mice experimentally infected with toxoplasmosis were treated with Daraprim (pyrimethamine) or supronal (equal parts of 2-[4′-aminobenzolsulfonamido]-4-methyl-pyrimidine and the 4-aminobenzolsulfothiocarbamide salt of the 4-aminomethylbenzolsulfonamide). Therapy with 11.25 mg Daraprim over a period of 5 days was successful in 50% of the infected mice while administration of 102 mg supronal in 6 days only delayed the death of the mice. A combined dose of 4 mg Daraprim and 45 mg supronal in 10 days cured 60% of the animals. Both drugs are poorly tolerated and many mice died from the effects of the therapy.

204. BUBE, F. W. Beiträge zum Nachweis und zur Behandlung der Kaninchencoccidiose. (Diagnosis and treatment of coccidiosis in rabbits.) *Zentr. Bakteriol. Parasitenk.* Abt. I Orig. 171: 363–71, 1958.

The mode of infection, pathological-anatomical signs and diagnosis of coccidiosis are described. Therapy with resochindiphosphate is reported. Microscopic demonstration of the protozoan in the feces may be supplemented by a complement-fixation test with a specific antigen.

205. CARMICHAEL, L. E. AND SARKAR, S. An indirect hemagglutination test for detecting infectious canine hepatitis virus antibodies. *Cornell Vet.* 48: 386–93 (Oct.), 1958.

The test is based upon the principle that agglutination occurs when homologous antiserum is incubated with virus which has been adsorbed onto the cell envelop of tannic-acid-treated sheep erythrocytes. The test should be run under specific conditions of pH and electrolytes. (From author's summary)

206. CHARLES, R. T. AND REES, O. Use of sulphonamides in the treatment of pleuro-pneumonia-like organisms in rats. *Nature* 181: 1213 (Apr. 26), 1958.

The syndrome of pleuropneumonia in rats is described. The disease may be controlled by treatment with triple sulfonamide, a mixture of equal parts of sulfamerazine, sulfadiazine and sulfapyridine as an 0.2% aqueous solution in the drinking water. These drugs are also being tested as prophylactic agents.

207. COHRS, P., JAFFE, R. AND MEESSEN, H., ed. *Pathologie der Laboratoriumstiere.* (*Pathology of Laboratory Animals.*) Berlin, Springer, 1958, 2 vols., 799 and 803 pp.

The following chapters are contained in vol. I and II: (I) circulatory system, respiratory system, digestive system, blood and hematopoietic organs, urogenital system, endocrine system, skeletal system, skin, sense organs, nervous system; (II) infectious diseases caused by bacteria and plant parasites, viral diseases, animal parasites and parasitic diseases, serological diagnosis of spontaneous diseases in small laboratory animals, environmental and nutritional diseases, hereditary diseases of rodents, gerontology, tumors, diseases of birds, diseases of fish, amphibia and reptiles.

208. Cook, J. E. Salivary-gland virus disease of guinea pigs. *J. Natl. Cancer Inst.* 20: 905–9 (May), 1958.

Salivary-gland virus disease of guinea pigs is apparently mild and specific for its natural host. Its presence is readily detected by histopathologic examination of tissue from diseased salivary glands in which the characteristic hypertrophy and intranuclear inclusion bodies are observed in the cells of the ductal epithelium. It is believed that the incidence of colony infection is directly related to the degree of sanitation practiced. (Author's summary)

209. Cornelius, C. E., Theilen, G. H. and Rhode, E. A. Quantitative assessment of bovine liver function, using the sulfobromophthalein sodium clearance technique. *Am. J. Vet. Research* 19: 560–6 (July), 1958.

A quantitative liver function test is described and used on 5 cattle suspected of having hepatopathy.

210. Cossel, L. Nierenbefunde beim Meerschweinchen bei Klossiellen-Infektion (Klossiella cobayae). (Zur Kenntnis der speziellen Pathologie der Versuchstiere.) (Kidney lesions in guinea pigs with *Klosiella cobayae*. Special pathology of the experimental animals.) *Schweiz. allgem. Pathol. u. Bakteriol.* 21: 62–73, 1958.

Guinea pigs experimentally infected with *Klosiella cobayae* did not show any externally noticeable signs of disease. Histological tests of the kidneys revealed several stages of schizogony, leading to a cyst in the epithelial cells.

211. Cox, D. H. and Baker, B. R. A diagnostic test for organic phosphate insecticidal poisoning of cattle. *J. Am. Vet. Med. Assoc.* 132: 385–7 (May 1), 1958.

A simple and rapid colorimetric test for blood cholinesterase is described as an aid, in conjunction with signs and history, in the diagnosis of suspected or actual cases of cattle poisoned by organic phosphate insecticides. (Author's summary)

212. Crain, R. C. Spontaneous tumors in the Rochester strain of the Wistar rat. *Am. J. Pathol.* 34: 311–5 (Mar.-Apr.), 1958.

Two hundred spontaneous tumors occurred in 189 out of 786 Wistar albino rats of the Rochester strain, aged 18–24 mo.; this is an incidence of about 25%. Primary tumors were found in all organs except those of the cardiovascular and locomotor systems; about ⅓ were malignant The most common tumors in the order of incidence were fibroadenoma of the breast, malignant lymphoma of the lung and mesenteric lymph nodes, and interstitial cell adenoma of testis.

213. Cronheim, G., Gourzis, J. T. and Toekes, I. M. New type sedative and soporific drug. *Science* 128: 1570–1 (Dec. 19), 1958.

Trimethoxybenzoyl-glycine-diethylamide induced in dogs and cats normal sleep without preceding ataxia. The oral soporific dose was 50 mg/kg, with a latency of 30–90 min. and a duration of 2–6 hr. A 5–10-fold increase of the dose resulted in restlessness and disorientation. No spindling or drug-induced artifacts were found in electroencephalographic recordings.

214. Davis, D. E. and Read, C. P. Effect of behavior on development of resistance in trichinosis. *Proc. Soc. Exptl. Biol. Med.* 99: 269–72 (Oct.), 1958.

Mice raised from a wild strain were infected with *Trichinella* and kept isolated or grouped for 10 days and killed after 15 and 30 days, respectively. The grouping procedure consisted of placing 6 mice together in a large can without food or water for 3–4 hr/day after which each mouse is put back in its own jar and kept isolated from other mice. There was vigorous fighting during the 1st day of the grouping but a social rank was established about the 3rd day. Controls were kept isolated throughout. The number of *Trichinella* found in controls and grouped mice was 0–16 and 16–51 worms, respectively, after 15 days, and 880–1273 and 1433–1733 worms, respectively, after 30 days. It is concluded that behavior may affect resistance and it is suggested that this phenomenon may be an important factor in epidemics and in development of host-parasite relations.

215. Detweiler, D. K. Chronic heart disease in dogs. In: *Chronic Diseases in Animals.* Atlanta, Ga., U. S. Public Health, Communicable Disease Center. 6th Ann. Health Conf., June, 1958, pp. 27–39.

Dogs are subject to a variety of cardiovascular disorders and chronic valvular diseases of aging. These diseases have a bearing on the usefulness of dogs in cardiovascular research.

216. Dikshit, P. K. and Sriramachari, S. Caudal necrosis in suckling rats. *Nature* 181: 63–4 (Jan. 4), 1958.

The nutritional status of the mother rats, particularly with regard to the essential fatty acid content of the stock diet, plays an important part in the development of ringtail in newborn rats. Besides inadequacy of fat, environmental factors such as relative humidity may also be influential.

217. Dolan, M. M., Kligman, A. M., Kobylinski, P. G. and Motsavage, M. A. Ringworm epizootics in laboratory mice and rats: Experimental and accidental transmission of infection. *J. Invest. Dermatol.* 30: 23–5 (Jan.), 1958.

Three laboratory workers contracted ringworm infections of the hands during mouse and rat experimental studies not concerned with mycology. Cultures of the hair of rats and mice immediately after arrival from breeding farms revealed that 18% of the animals harbored *Trichophyton mentagrophytes*. No gross evidence of infection was present in these groups of animals. Some prophylactic procedures for limiting the spread of infections among animals and humans are suggested. (Condensed from authors summary)

218. Dubos, R. J. and Schaedler, R. W. Effect of dietary proteins and amino acids on the susceptibility of mice to bacterial infections. *J. Exptl. Med.* 108: 69–81 (July), 1958.

Groups of young albino mice were fed 4 different types of diets, providing an adequate supply of minerals and vitamins. After different periods of time on these regimens, the animals were infected by intravenous injections with *Staphylococcus aureus*, *Mycobacterium fortuitum* or *Mycobacterium tuberculosis bovis*. The differences in susceptibility exhibited by the mice on the 4 diets were the same

whatever the species of bacterial pathogen used, the size of the dose and the duration of the disease.

219. DUNNE, H. W., ed. *Diseases of Swine.* Ames, Iowa State Univ. Press, 1958, 716 pp.

The book is divided into the following sections: Anatomy and physiology (including hematology and hematopoietic organs); viral diseases; parasitic infections; toxemias and poisonings; miscellaneous diseases; surgery; nutrition, feeds and management.

220. EMMONS, C. W. Association of bats with histoplasmosis. *Public Health Repts. (U.S.)* 73: 590–5 (July), 1958.

Histoplasma capsulatum was isolated from 50 of 105 soil samples from 6 collections made between October 1956 and September 1957 on the premises where a family epidemic of histoplasmosis had occurred. Chickens, often associated with the saprophytic growth of this fungus, had not been kept on the premises for many years. *Histoplasma* was isolated from 45 of 66 soil specimens (68%) taken adjacent to or within 5 ft. of the foundation wall of the house and from only 2 of 29 (6.8%) taken 6–18 ft. from the house. Three of 10 samples taken near a doghouse were also positive. The house sheltered a colony of the brown, or house, bat (*Eptesicus fuscus*), and bat dung was found adjacent to the foundation. The presence of bats is the apparent factor responsible for the constant saprophytic infestation of soil on these premises with *H. capsulatum*. (Condensed from author's summary)

221. FISCHER, W. AND KÜHL, I. *Geschwülste der Laboratoriumsnagetiere.* (*Tumors of Laboratory Rodents.*) Dresden, Steinkopf, 1958, 260 pp.

The book contains the following chapters in part *A*: Tumors, spontaneous and experimental, of the respiratory tract, liver, kidney and urinary passages, male and female genital organs, mammary gland, thyroid, adrenal, heart and vascular system, thymus and hematopoietic organs, neoplasms of the hematopoietic and reticuloendothelial systems, tumors of bones and muscles, skin, brain and spinal cord, ascitic sarcoma of the rat, Ehrlich's ascitic carcinoma. In part *B* general topics are discussed such as cellular reactions in spontaneous and experimental tumors, resistance and immunity to tumors.

222. FLINT, J. C., ROEPKE, M. H. AND JENSEN, R. Feline infectious anemia. I. Clinical aspects. *Am. J. Vet. Research* 19: 164–8 (Jan.), 1958.

Feline infectious anemia is an acute or chronic blood parasite disease characterized by emaciation, depression, anorexia, and a high initial temperature, with rapid development of a macrocytic, hemolytic anemia which produces a characteristic blood picture. Data on 30 clinical cases are reported in this phase of the investigation. It is believed the etiological agent is a member of the genus *Hemobartonella*. The organisms appear as small cocci or rods on the erythrocytes of blood smears stained with Giemsa's or Wright's stains. Diagnosis is based on many factors which are not pathognomonic. The method of transmission has not been determined. The mortality varies greatly. Comparatively few therapeutic agents have been tried in treating the disease. (Condensed from author's summary)

223. FOSTER, H. L. Purulent keratoconjunctivitis in laboratory rats, caused by *Micrococcus pyogenes var. aureus*. *J. Am. Vet. Med. Assoc.* 133: 201 (Aug. 15), 1958.

An acute and subacute infectious ocular disease of rats, spread from rat to rat, and possibly by animal handlers, has been observed on different occasions and in a large number of young rats—never in adult animals. It occurs most frequently in recently weaned animals, but infection can arise during the lactation period and affect several in a litter. The condition can be controlled by local application of ophthalmic ointment containing chlortetracycline (aureomycin).

224. FOSTER, H. L. Comparison of epizootic diarrhea of suckling rats and a similar condition in mice. *J. Am. Vet. Med. Assoc.* 133: 198–201, (Aug. 15), 1958.

The clinicopathological features of epizootic diarrhea of suckling mice are compared with those seen in suckling rats. In the rat, as in the mouse, there are no gastroenteric lesions to account for the diarrhea, and no "viral" inclusion bodies either in nuclei or cytoplasm of intestinal epithelium have been unequivocally demonstrated. Some cytoplasmic "inclusions" illustrated might more likely be secretory products. Attempts to transmit the disease by intestinal filtrates failed. (Condensed from author's summary)

225. FREDRICKSON, T. N. AND CHUTE, H. L. Further studies of chicken blood tests and their application. *Avian Diseases* 2: 241–9, 1958.

Normal values are given for 10 different blood tests on broiler chickens, day-old to 10 wk. of age. Upwards of 400 broilers were examined. In Newcastle disease the white blood cell and leukocyte differential count were of the greatest diagnostic value. The erythrocyte sedimentation rate, buffy coat values and plasma specific gravity were also altered during the disease. (*Vet. Bull.* 29: Abstr. No. 733, 1959)

226. FRITZSCHE, K. AND UNRUH, W. Untersuchungen über eine Verbesserung der Technik der Tuberkulin-Kehllappenprobe beim Huhn. (Improvement of the technique for the wattle tuberculin test in fowls.) *Berlin. u. Münch. tierärztl. Wochschr.* 71: 303–5, 1958.

A single tuberculin injection gives no reliable results. Three injections of 0.1 cc on 3 successive days are recommended in order to obtain reliable results.

227. GENTLES, J. C. Experimental ringworm in guinea pigs: oral treatment with griseofulvin. *Nature* 182: 476–7 (Aug.), 1958.

Guinea pigs, experimentally infected with *Microsporum canis* and treated 10 days later with daily oral doses of 60 mg griseofulvin/kg, showed a beneficial effect within 4 days. Oral administration of griseofulvin was equally effective in guinea pigs experimentally infected with *Trichophyton mentagrophytes*. *In vitro* it is active in low concentrations against all common dermatophytes.

228. GENTRY, R. F. Virus induced tumors. In: *Chronic Diseases in Animals.* Atlanta, Ga., U. S. Public Health, Communicable Disease Center. 6th Ann. Health Conf., June, 1958, pp. 1–7.

A primary characteristic of virus-induced tumors is the extended latent period or incubation time. Detection of latest infection is difficult and will depend upon improved technique with electron microscopy and serology. Some of the tumors known to be associated with viruses include human skin tumors, mouse mammary carcinoma, tumors of fish and plants, mouse leukemia, and avian tumors, especially visceral lymphomatosis. Avian visceral lymphomatosis has been studied as much or more than the other tumors and serves as the best subject for the discussion of transmission and control. (Condensed from author's abstract)

229. GILBERT, C., GILLMAN, J., LOUSTALOT, P. AND LUTZ, W. The modifying influence of diet and the

physical environment on spontaneous tumour frequency in rats. *Brit. J. Cancer* 12: 565–93 (Dec.), 1958.

The influence of diet and geographical origin on the kind and frequency of spontaneous neoplasms in 3 strains of Wistar albino rats was investigated. GG strain rats reared in Johannesburg and 2 migrant strains, Utrecht and Copenhagen, were used.

230. GILLESPIE, J. H., BAKER, J. A., BURGHER, J., ROBSON, D. AND GILMAN, B. The immune response of dogs to distemper virus. *Cornell Vet.* 48: 103–26 (Apr.), 1958.

The test in eggs for distemper-neutralizing antibodies in dog serums was shown to be specific and accurate if the amount of the virus used in the test was controlled. Virus neutralization compared with test by virulent virus showed that all 420 dogs studied that were immune to distemper had neutralizing antibodies, whether the immunity resulted from infection or was acquired from the mother either by *in utero* transfer or through the intake of colostrum. Most puppies 1 wk. of age or older responded to virulent distemper virus either by dying or by developing immunity if they showed a serum titer of less than 20. They were immune if their titers were higher than 30. The serum titer of a puppy was found to be proportional to the serum titer of its mother; in a puppy before nursing it was approximately 3% of the mother's serum titer and after intake of colostrum about 77% of the colostral titer, which reflected the mother's serum titer. A nomograph was constructed which permits, on the basis of the serum titer shown by a pregnant dog, a prediction of the age at which puppies as yet unborn could be immunized and thereby make available maximum protection from vaccine by vaccination at the earliest possible age. (Condensed from author's summary)

231. GRIESEMER, R. A. Bartonellosis. *J. Natl. Cancer Inst*, 20: 949–55 (May), 1958.

The microorganisms commonly referred to as bartonella may be divided into 2 genera, *Bartonella* and *Haemobartonella*. The *Bartonellae* are parasites of the erythrocytes and fixed tissue cells of man. The *Haemobartonellae* are parasites of the erythrocytes but not of other tissue cells, occurring naturally in vertebrates other than man, and transmitted by arthropods. The organisms are very polymorphous but are predominantly rod or coccoid forms showing no differentiation into nucleus and cytoplasm. Almost all species of this genus are world-wide in distribution but rarely produce disease in animals without splenectomy. Bartonellosis is most severe in the rat in which an acute hemolytic anemia is produced by splenectomy of carrier animals.

232. GRUNT, J. A., BERRY, R. J. AND KNISELY, W. H. Age and castration in relation to fatty liver in the male rat. *Endocrinol.* 62: 822–7 (June), 1958.

At necropsy, 20 of 21 male rats aged 571–821 days had grossly fatty, enlarged livers. By contrast, 24 aged neonatal castrates did not demonstrate this finding. The livers of 24 younger animals, 77–173 days, from comparable treatment groups, were not grossly fatty. Extracted liver fat and histologic findings paralleled the gross findings of fatty and nonfatty livers. (Condensed from author's summary)

233. GRUNT, J. A., BERRY, R. J. AND KNISELY, W. H. Effects of castration and/or hormonal therapy upon the hematocrit in aged male rats. *J. Gerontol.* 13: 359–61 (Oct.), 1958.

Hematocrit was only slightly decreased in old age. Castration produced a pronounced fall in hematocrit in aged animals. The hematocrit of aged neonatal castrates was similar to that of young adult neonatally castrated animals.

234. GUTEKUNST, R. R. Studies on canine pleuropneumonia-like organisms. Thesis, Cornell, 1958, 45 pp.

Attempts to isolate pleuropneumonia-like organisms (PPLO) were made on 35 dogs with respiratory illness and on 25 dogs with no respiratory illness. Fifty-two strains of PPLO were discovered from the 1st group of dogs. Growth of 46 of these strains resulted in the formation of 5 distinct colonial types. Pathogenicity for mice was established with 14 strains of canine PPLO but attempts to produce disease in 21 beagle puppies were successful only in 1 instance. (From *Dissertation Abstr.* 19: 2214, 1959)

235. HABERMANN, R. T. AND WILLIAMS, F. P., JR. Salmonellosis in laboratory animals. *J. Natl. Cancer Inst.* 20: 933–47 (May), 1958.

Salmonellosis in mice, rats, guinea pigs, rabbits, hamsters, monkeys and dogs and its treatment and prevention are discussed. Diagnostic tests for salmonellosis are reviewed.

236. HABERMANN, R. T. AND WILLIAMS, F. P., JR. The identification and control of helminths in laboratory animals. *J. Natl. Cancer Inst.* 20: 979–1009 (May), 1958.

The identification of helminths in mice, rats, guinea pigs, hamsters, rabbits, monkeys, dogs and cats, factors which interfere with the diagnosis, and laboratory techniques for the diagnosis are discussed. Characteristics of tapeworms in mice, rats, dogs and cats and roundworms in mice, rats, guinea pigs, rabbits, rhesus monkeys, dogs and cats are reviewed. Control measures are suggested.

237. HAGEN, K. W., JR. The effect of continuous sulfaquinoxaline feeding on rabbit mortality. *Am. J. Vet. Research* 19: 494–6 (Apr.), 1958.

Since sulfaquinoxaline is an efficient drug for the control of the liver type of coccidiosis in rabbits and *Pasteurella multocida* infection in poultry, the effect of continuous feeding of sulfaquinoxaline on rabbit mortality was studied. A ration containing 0.025% of the drug fed over 12 mo. had no toxic effects and was palatable. The hemorrhagic type of enteritis in sulfaquinoxaline-fed rabbits was 70% less than in controls. Deaths by primary pneumonia was eliminated and *Pasteurella multocida* infections were reduced by 70%. Nestbox mortality was reduced when the drug was given to the doe and the 14-day-old litter.

238. HALEY, A. J. Host specificity of the rat nematode, *Nippostrongylus muris*. *Am. J. Hyg.* 67: 331–49 (May), 1958.

The objectives of the present investigation were: *1*) to obtain a quantitative estimate of the difference in the resistance of rats and hamsters to infection with *N. muris*; *2*) to characterize the differences in the behavior of the parasite in these two hosts; and *3*) to determine if, and to what extent, the specificity of *N. muris* could be modified by passage of the parasite in the abnormal host.

239. HARE, W. C. D. Radiographic anatomy of the canine skull. *J. Am. Vet. Med. Assoc.* 133: 149–57 (Aug. 1), 1958.

Illustrations are given to be used as a guide in the interpretation of radiographs of the canine skull.

240. ISLER, H., LEBLOND, C. P. AND AXELRAD, A. A. Influence of age and iodine intake on the production of thyroid tumors in the rat. *J. Natl. Cancer Inst.* 21: 1065–81 (Dec.), 1958.

The influence of age and I intake on the production of neoplastic thyroid nodules was investigated in 1-, 4- and 14-mo.-old Sherman rats fed for 12 mo. on a low I diet with or without I supplement.

241. JAKWAY, J. S. AND YOUNG, W. C. An inherited spermatogenic hypoplasia in the guinea pig. *Fertility and Sterility* 9: 533–44, 1958.

Mating tests were performed in guinea pigs and the testes and epididymides were studied microscopically. Defects were found ranging from germinal aplasia in most of the seminiferous tubules to a slightly subnormal state in which the germinal epithelium appeared to be normal, but spermatozoa in the epididymides were massed singly rather than in extensive rouleaux formation. An estimated 30%–50% of the males were affected. (From author's summary)

242. KAPLAN, H. M. Treatment of escherichiosis in turtles, frogs and rabbits. *Proc. Animal Care Panel* 8: 101–6 (Sept.), 1958.

Chloramphenicol, given by various routes, in dosages involving an initial priming dose of 6 mg/100 gm of living body weight, followed by 3 mg/100 gm twice daily for 7 days, produced marked improvement in the structure of the red blood cells and in the general health in turtles, frogs and rabbits infected naturally or experimentally with *Escherichia freundii*. This pathogen causes in nature a disease, primarily of turtles, which has now been termed "escherichiosis." (Author's summary)

243. KENT, S. P. AND PICKERING, J. E. Neoplasms in monkeys (*Macaca mulatta*): spontaneous and irradiation induced. *Cancer* 11: 138–47 (Jan.-Feb.), 1958. (Also *U.S. Air Force, School of Aviation Medicine Rept.* 57–110, June, 1958.)

The neoplasms noted in more than 450 monkey autopsies are reported. The 9 neoplasms found were a fibroma, papillomas of the stomach, a hemangioendothelioma, a pituitary adenoma, an osteosarcoma, a malignant lymphoma, a glioblastoma multiforme, and 2 fibrosarcomas. The first 6 developed in animals that had not been exposed to a known carcinogen or had been exposed under circumstances that suggested that the carcinogen was not related to the development of the neoplasms. The last 3 malignant neoplasms occurred in animals receiving high doses of focal ionizing radiation under circumstances that suggested that the appearance of the neoplasm was related to the irradiation. The glioblastoma multiforme and the malignant lymphoma are the first reported cases of these types of neoplasms in monkeys. (Author's summary)

244. LEE, H. W.-T. AND MOINUDDIN, J. F. Effects of oral chlortetracycline on diarrhea and on the dry weights of cleaned intestinal organs in rats fed two different diets. *Am. J. Physiol.* 192: 421–6 (Feb.), 1958.

When groups of weanling male Sprague-Dawley rats were fed a basal cornstarch and a 25% lactose diet, many of the lactose-fed rats developed diarrhea during the first 2 weeks. Feeding chlortetracycline HCl (30 mg/kg of diet) did not affect the number of fecal discharges. The body weight, weights of cleaned organs (small intestine, cecum, colon + rectum), length of small intestine and the weight:length ratio of the small intestine for the cornstarch and lactose-fed group, with and without chlortetracycline, are reported.

245. LINDT, S. Über Krankheiten des syrischen Goldhamsters (*Mesocricetus auratus*). (Diseases of the Syrian golden hamster (*Mesocricetus auratus*).) *Schweiz. Arch. Tierheilk.* 100: 86–97, 1958.

Diseases were studied in 130 golden hamsters. The incidence (%) was as follows: trauma 26, digestive tract and liver 15, skin changes 15, tumors 10, respiratory 8, ocular 8, genital 6, miscellaneous (neurological, infections) 12.

246. LONSDALE, F. Ringworm in animals. *J. Animal Technicians Assoc.* 9: 14–6 (June), 1958.

The disease of ringworm is discussed and it is pointed out that at present the only way of reducing this hazard consists in extreme cleanliness of the animal house.

247. MCKEEVER, S., KAPLAN, W. AND AJELLO, L. Ringworm fungi of large wild mammals in southwestern Georgia and northwestern Florida. *Am. J. Vet. Research* 19: 973–5 (Oct.), 1958.

In hair specimens of 1758 large wild mammals only 1.1% were found to contain ringworm fungi. Lack of any evidence of infection in animals from which dermatophytes were isolated indicates that the fur of these animals may have been contaminated with spores from the environment, rather than being infected. *Microsporum gypseum* was recovered from 13 of 189 soil samples from areas trapped. (Condensed from author's summary)

248. MCKEEVER, S., MENGES, R. W., KAPLAN, W. AND AJELLO, L. Ringworm fungi of feral rodents in southwestern Georgia. *Am. J. Vet. Research* 19: 969–72 (Oct.), 1958.

In hair specimens collected from 996 feral rodents 11.4% were found to yield dermatophytes or dermatophyte-like fungi. However, direct microscopic and Wood's lamp examinations were negative. The fungi obtained were *Trichophyton mentagrophytes*, *Microsporum gypseum* and a red variety of *Microsporum*. The fungus is not pathogenic to man or lower animals. The animals tested were merely carriers of the fungus. The percentage of host animals in the various habitats increased with the progression of plant succession toward pure pine. The occurrence of the fungi in different environments is discussed.

249. MALHERBE, H. AND MUNDAY, V. *Encephalitozoon cuniculi* infection of laboratory rabbits and mice in South Africa. *J. S. African Vet. Med. Assoc.* 29: 241–6, 1958.

The symptoms of *Encephalitozoon cuniculi* in rats and mice and the occurrence of this disease in South African laboratories is reported. Infection with this parasite should be borne in mind when rodents are inoculated with material thought to contain neurotropic agents.

250. MAURER, F. D. Lymphocytic choriomeningitis. *J. Natl. Cancer. Inst.* 20: 867–70 (May), 1958.

The virus causing lymphocytic choriomeningitis has been isolated from laboratory and house mice, monkeys, dogs, guinea pigs, roaches, ticks and man. Experimental infection has been established in man, chimpanzees, monkeys, guinea pigs, rats, mice, dogs and small pigs. Most colonies of laboratory mice harbor the virus, but most of the infected mice carry the disease in a latent form. Signs of infection, gross and microscopic findings, detection and control of the disease are discussed.

251. MAURER, F. D. Mouse poliomyelitis or Theiler's mouse encephalomyelitis. *J. Natl. Cancer Inst.* 20: 871–4 (May), 1958.

The virus causing Theiler's mouse encephalomyelitis is present in the intestinal tract of about ⅔ of apparently normal white mice

from 1–6 mo. of age; in very rare cases an infection of the central nervous system occurs. A natural immunity is acquired with age. Atrophy of muscles is the only grossly apparent change; microscopic studies show necrosis of the ganglionic cells of the anterior horn.

252. MILLAR, M. J., FISCHER, M. I., ELCOATE, P. V. AND MAWSON, C. A. The effects of dietary zinc deficiency on the reproductive system of male rats. *Can. J. Biochem. Physiol.* 36: 557–69, 1958.

Dietary zinc deficiency produced by feeding a zinc-poor diet (0.5 μg zinc/gm) to weanling rats for 8 wk. caused marked retardation in body growth, depressed growth and development of testes, epididymides, accessory sex organs, and pituitary glands, and in many cases severe atrophy of testicular germinal epithelium. The zinc concentration of dorsolateral prostates, testes, epididymides, and bone was reduced in zinc-deficient rats compared with controls receiving the zinc-poor diet plus 100 μg zinc daily. All the observed changes produced by zinc deficiency except the testicular atrophy were reversed when zinc was replaced in the diet. If testicular atrophy had occurred, neither testis nor epididymis regained normal size, function, or zinc concentration. (Condensed from author's summary)

253. NEHER, G. M. Experimental production of rheumatoid arthritis in swine. In: *Chronic Diseases in Animals.* Atlanta, Ga., U.S. Public Health Service, Communicable Disease Center. 6th Ann. Health Conf., June, 1958, pp. 9–26.

An economically important disease that bears many similarities to rheumatoid arthritis occurs naturally in swine. It can also be produced experimentally in susceptible pigs following exposure to the bacterium *Erysipelothrix rhusiopathiae*. Although rheumatoid arthritis in man and swine have no common etiologic agent, the arthritic pig may prove to be a useful test animal for the screening of antiarthritic drugs and hormone preparations.

254. NELSON, J. B. Infection in laboratory animals with pleuropneumonia-like organisms. *J. Natl. Cancer Inst.* 20: 911–9 (May), 1958.

Organisms of the pleuropneumonia group (PPLO) are widely distributed in rats and mice and many different types are recognized. Infectious catarrh, a chronic disease that involves the nasal passages, middle ears, and lungs, is produced by PPLO in rodents. The disease is transmissible by direct contact and is prevalent in breeding colonies. Other organs in mice or rats, which PPLO may frequent naturally or experimentally, are the conjunctiva, the brain, the joints, and the female genitalia. Localization of the organisms is usually attended by an infiltration of leukocytes and exudation. PPLO are recoverable from all loci of involvement by cultivation on nutrient agar enriched with horse serum. (Author's summary)

255. NEWBERNE, P. M. AND O'DELL, B. L. Histopathology of hydrocephalus resulting from a deficiency of vitamin B_{12}. *Proc. Soc. Exptl. Biol. Med.* 97: 62–5 (Jan.), 1958.

Weanling female rats of the Wistar strain, fed a vitamin B_{12} deficient diet through the reproductive phase, produced offspring with a high incidence of hydrocephalus. The significant observations were that the ependymal lining and choroid plexus were deranged and contained excess lipids.

256. NIKOLITSCH, M. Zur Diagnostik der Aujeszky'schen Krankheit. (Diagnosis of Aujeszky's disease.) *Arch. Hyg. u. Bakteriol.* 142, No. 2: 93–8, 1958.

The white mouse is not a suitable animal for the diagnosis of Aujeszky's disease (pseudorabies) regardless of whether the test material is inoculated by the intracerebral or intramuscular route. More characteristic symptoms are obtained when the pseudorabies virus is inoculated i.m. into rabbits or guinea pigs.

257. NIKOLITSCH, M. Kontaktinfektion bei der Aujeszky'schen Krankheit. (Contact infection in Aujeszky's disease.) *Arch. Hyg. u. Bakteriol.* 142, No. 5: 347–50, 1958.

The route of infection of the pseudorabies virus was studied experimentally in rabbits. The results of the experiments point to infection by contact as the most probable route.

258. O'DELL, B. L., MORRIS, E. R. AND REGAN, W. O. Effect of phosphorus on magnesium requirement. *Federation Proc.* 17: Abstr. No. 1910 (Mar.), 1958.

Rats and guinea pigs were fed diets deficient in magnesium and containing variable quantities of calcium and phosphorus. A high intake of phosphorus accentuated the symptoms of magnesium deficiency in both species to as great an extent if not greater, than high levels of calcium. Rats showed signs of hyperemia, skin lesions and nervous disorders while in guinea pigs a derangement of the calcification process was the most significant sign. All gross symptoms in both rat and guinea pig were aggravated by high P intake.

259. PAPPENHEIMER, A. M. Epidemic diarrheal diseases of suckling mice. *J. Natl. Cancer Inst.* 20: 861–5 (May), 1958.

Diarrheal disease of viral etiology in suckling mice may cause heavy mortality in breeding colonies (*see* Cheever, F. S. and Mueller, J. H.; Syverton, J. T. and Olitsky, P. K.). At least 2 different agents were found to be responsible for the disease. One was characterized by the occurrence of intranuclear inclusions, the other by cytoplasmic ones. The virus has not yet been studied in detail. Author points out that cytoplasmic inclusions of larger size have been found in healthy mice at different ages, but these inclusions appeared unrelated to the diarrheal disease.

260. PAPPENHEIMER, A. M. Pathology of infection with the JHM virus. *J. Natl. Cancer Inst.* 20: 879–91 (May), 1958.

A disseminated encephalomyelitis in mice characterized by widespread destruction of myelin in brain and cord, and produced by the JHM virus is described. An infection of mice with DA virus and a demyelinating disease in rats are also reported.

261. PAPPENHEIMER, A. M. Myocarditis and pulmonary arteritis associated with the presence of rickettsia-like bodies in polymorphonuclear leukocytes. *J. Natl. Cancer Inst.* 20: 921–31 (May), 1958.

Some 200 mice were inoculated with the suspected active agent. Besides the occurrence of myocarditis, lesions were noted in many interpulmonary branches of the pulmonary arteries. A clue to the etiology of these lesions was afforded by the finding of minute coccobacillary bodies within the cytoplasm of the polymorphonuclears. A rickettsial nature of these bodies could not be proved conclusively.

262. PEREZ GALLARDO, F., ZARZUELO, E. AND KAPLAN, M. M. Local treatment of wounds to prevent rabies. *Bull. World Health Organization* 17: 963–78, 1958.

Methods of producing wounds in guinea pigs and infecting them with street virus, and local treatment of these wounds with

XUM

nitric acid, detergent solution or antirabies serum for the prevention of rabies are reported. The lethality of virus suspensions with and without hyaluronidase was studied.

263. RUBIN, M. L. Studies on toxoplasmosis. *Am. J. Trop. Med. Hyg.* 7: 358–64 (July), 1958.

Several antimalarial drugs were tested for effectiveness in prolonging the life of mice after infection with a highly lethal dose of *Toxoplasma* (RH strain). Oral or subcutaneous drug administrations were employed. None of these (Plaquenil, Aralen, and primaquine) showed any effect. Various sulfonamide compounds, both alone and in combination with pyrimethamine, were tested as drug cures. The most effective combinations were sulfapyrazine-pyrimethamine, and sulfadiazine-pyrimethamine mixtures, substantiating the work of Eyles and others. Another double-sulfa mixture (sulfamylon and sulfamerazine) was tested and also found to be very effective as a drug cure in acute toxoplasmosis, especially when used with pyrimethamine. These experiments also demonstrated the synergism existing between certain sulfonamides and pyrimethamine against toxoplasmosis in mice. (Condensed from author's summary)

264. ST. GEORGE-GRAMBAUER, B. M. Disease of laboratory mice. *J. Animal Technicians Assoc.* 9: 43–9 (Dec.), 1958.

Among the 481 sick or abnormal mice studied during 12 mo. in the breeding colony of the Queensland Institute of Medical Research, the commonest conditions found were megacolon (83), chronic inflammation of the lungs (57), *Corynebacterium murium* abscesses of lungs (29) and of liver (12), Tyzzer's disease of liver (21), *Streptobacillus moniliformis* infection (17), hydrocephalus (15), spinal deformity (8), muscle necrosis (6), volvulus (6), intussusception (5). Tumors found included mammary adenocarcinoma (10), lymphosarcoma (2), ovarian teratoma (1), ovarian cystadenoma (1). All these were in mice at least 6 mo. of age. The morbidity was highest in July, Aug. and Sept. when infectious diseases were most prevalent. In 78 cases necropsy did not disclose the cause of illness. (Author's summary)

265. SAUNDERS, L. Z. Mouse pox (infectious ectromelia). *J. Natl. Cancer Inst.* 20: 875–7 (May), 1958.

Mouse pox, caused by a filtrable virus, is highly infectious and often epizootic. All strains of mice are susceptible, but rats, rabbits and guinea pigs are resistant. Signs, diagnosis and control of the disease are discussed.

266. SAUNDERS, L. Z. Tyzzer's disease. *J. Natl. Cancer Inst.* 20: 893–7 (May), 1958.

Tyzzer's disease in mice is associated with *Bacillus piliformis* and is characterized by focal necrosis of the liver. There are few survivors among young animals while in old mice the mortality rate is low. Histologic findings are described. The disease may be controlled by environmental factors.

267. SAUNDERS, L. Z. Myositis in guinea pigs. *J. Natl. Cancer Inst.* 20: 899–903 (May), 1958.

A disease characterized by inflammation of the skeletal muscles occurred in a colony of guinea pigs. The cause was not determined, but it could be distinguished histologically from other diseases of guinea pigs which are characterized by impaired locomotion. (Author's summary)

268. SCOTT, H. G. Control of mites on hamsters. *J. Econ. Entomol.* 51: 412–3 (June), 1958.

By treating the removable tray at the bottom of each cage with an emulsion of 2% chlordane each time the cages were washed, the mite population was reduced to 3/animal within 2 wk. Continued painting with chlordane and subsequent spraying with 0.3% pyrethrin: 1.5% piperonyl butoxide solution controlled the remaining mites. The mites could also be efficiently controlled by dusting the hamsters with 0.11% lindane: 1.91% methoxychlor.

269. SCOTT, M. G. AND SCOTT, P. P. Some factors affecting the maturation of the reproductive organs of the cat. *Studies on Fertility* 9: 72–89, 1958.

The weights and histological appearances of the reproductive organs of healthy cats were compared with those in cats of subnormal growth due to respiratory or enteric infection or to malnutrition. Kittens suffering from chronic infection and malnutrition showed a retarded growth of the gonads and secondary sex organs together with a diminished output of testosterone and estrogen, respectively. In chronically infected adult cats regression or atrophy of the gonads was noted. The effects of infection and malnutrition on the genital organs could be reversed by treatment with antibiotics.

270. SHARP, C. F. Laboratory diagnosis of leptospirosis with the sensitised-erythrocyte lysis test. *J. Pathol. Bacteriol.* 76: 349–56 (Oct.), 1958.

An erythrocyte-sensitizing substance prepared from *L. australis* A (Strain Ballico) reacted with antibody against 26 pathogenic serotypes of leptospirae and the nonpathogenic serotype *L. biflexa*. A rising titer of erythrocyte-sensitizing substance (E.S.S.) antibody was detected by the sensitized erythrocyte lysis test in 104 patients with proved leptospiral infection. The test on paired sera appears to be of value in the diagnosis of leptospirosis, particularly when an epidemic necessitates the examination of large numbers of patients. The test may also aid in distinguishing active from anamnestic agglutination-lysis reactions, but its value as a means of surveying populations for past leptospiral infection is doubtful. The test is described only for man but may be applicable to laboratory animals. (Author's summary modified)

271. SIDRANSKY, H. AND FARBER, E. Chemical pathology of acute amino acid deficiencies. I. Morphologic changes in immature rats fed threonine-, methionine-, or histidine-devoid diets. II. Biochemical changes in rats fed threonine- or methionine-devoid diets. *A.M.A. Arch. Pathol.* 66: 119–34, 135–49 (Aug.), 1958.

Sprague-Dawley rats, force-fed purified diets devoid in threonine or histidine, developed a periportal fatty liver, excess hepatic glycogen, pancreatic edema and atrophy, and atrophy of salivary glands, gastric mucosa, and adrenal cortex within 7 days after beginning the diets. Rats force-fed a methionine-devoid diet showed periportal fatty liver but few of the other pathologic changes. Animals fed the same diets ad libitum, in contrast to those force-fed, consumed less food and showed no specific pathologic changes. The differences in the results between the force feeding and the ad libitum feeding regimens are explained in terms of the different quantity of the deficient diets consumed. The lesions observed in the rats force-fed threonine- or histidine-devoid diets resembled those reported to be characteristic of kwashiorkor. (Author's summary)

272. SILBERBERG, R., GOTO, G. AND SILBERBERG, M. Degenerative joint disease in castrate mice. I. Effects of ovariectomy at various ages. *A.M.A. Arch. Pathol.* 65: 438–41 (Apr.), 1958.

In female mice of strain C57BL, castration performed at 1, 6, or 12 mo. of age retarded articular aging and delayed the onset, decreased the incidence, and attenuated the course of osteoarthritis as compared to conditions seen in untreated controls.

These effects were most marked in animals spayed during early adulthood. (Condensed from author's summary)

273. SILBERBERG, R., THOMASSON, R. AND SILBERBERG, M. Degenerative joint disease in castrate mice. II. Effects of orchiectomy at various ages. *A.M.A. Arch. Pathol.* 65: 442–4 (Apr.), 1958.

Orchiectomy performed in sexually immature male mice of strains C57BL and DBA significantly delayed articular aging and attenuated the evolution of osteoarthritis as compared to the course of events in noncastrates. Orchiectomy carried out in adult male mice was less effective than castration performed early in life. (Condensed from author's summary)

274. SLANETZ, C. A. Is it possible to maintain a *Salmonella*-free colony of mice? *Proc. Animal Care Panel* 8: xx (Mar.), 1958.

A number of research workers have reported that it is possible to maintain a *Salmonella*-free mouse colony for considerable periods of time, up to several years, if certain precautions are observed. A closed colony system of breeding must be followed, careful attention given to feed and bedding supply, and frequent checks made by suitable culture methods for salmonella organisms in both the animals and feed. With regard to cultural methods, no standard procedure has been adopted to date but many laboratories have found the steroid-stress method a valuable aid. Mice are injected s.c. with 2.5 mg of hydrocortisone on 2 successive days. If *Salmonella* organisms or other bacterial pathogens are present, the animals die within approximately 2 wk. Frequent checks on the parent stock mice are desirable. It is important to maintain the colony under high animal husbandry standards.

275. SOBEK, V., JANKU, I., LOJDA, A. AND WENKE, M. Nebennierenrindeaktivation nach chronischer Chlortetrazyklinzufuhr bei Ratten. (Activation of the adrenal glands after prolonged administration of chlortetracycline to rats.) *Arch. intern. pharmacodynamie* 115: 397–401, 1958.

Ten rats were given food containing 0.01% chlortetracycline for a month. Ten rats were kept as untreated control. At the end of the month the adrenal glands of the treated rats weighed more than those of the controls. Histologically, the intermediate zone appeared to be absent in 80% of the treated rats.

276. SOKOLOFF, L. Joint diseases of laboratory animals. *J. Natl. Cancer Inst.* 20: 965–77 (May), 1958.

Degenerative joint disease (osteoarthritis), infectious arthritis and miscellaneous articular diseases (fractures, congenital anomalies, necrosis, chronic idiopathic synovitis and tenosynovitis, leukemic infiltration of synovial membrane) in mice, rats, guinea pigs, hamsters and rabbits are discussed.

277. SOKOLOFF, L. AND HABERMANN, R. T. Idiopathic necrosis of bone in small laboratory animals. *A.M.A. Arch. Pathol.* 65: 323–30 (Mar.), 1958.

Localized areas of spontaneous, apparently aseptic necrosis of bone have been observed in 31 of 670 mice during the 2nd yr. of life. The etiology is obscure, but the lesions appear to be influenced by genetic factors and sex. Isolated instances occurred in rats and a hamster. The lesions at times healed completely or were complicated by fracture of the femoral neck, collapse of epiphyses, kyphosis, or localized osteosclerosis simulating a bone tumor. The ossicles of the knees of a large proportion of all older rats and mice studied had a comparable pattern of necrosis. (Author's summary)

278. SPRENT, J. F. A. Observations on the development of *Toxocara canis* (Werner, 1782) in the dog. *Parasitology* 48: 184–209 (June), 1958.

Observations on the development of *Toxocara canis*, as observed in natural infections and in infections produced by feeding pregnant bitches with embryonated eggs, are reported. Two methods for searching the tissues of the dogs for larvae are discussed.

279. STEPHENSON, H. C. AND MITTELSTAEDT, S. G., ed. *Veterinary Drug Encyclopedia and Therapeutic Index; A Listing of Veterinary Drugs, Biologicals and Foods, and Feed Additives of American Manufacturers.* 6th ed. New York, Drug Publications, 1958, 412 pp.

The contents are arranged under the following sections: drugs, biologicals and foods (description, action and uses, administration and supply); cat and dog foods; feed additives; feed additives manufacturers' directory; feed additives index; manufacturers' directory and index; therapeutic index. Published every 1–2 yr.

280. STOENNER, H. G., GRIMES, E. F., THRAILKILL, F. B. AND DAVIS, E. Elimination of *Leptospira ballum* from a colony of Swiss albino mice by use of chlortetracycline hydrochloride. *Am. J. Trop. Med. Hyg.* 7: 423–6 (July), 1958.

Leptospira ballum apparently was eradicated from a large colony of Swiss albino mice by feeding pelleted feed containing 1,000 gm chlortetracycline hydrochloride/ton for 10 days. After 7 days of such therapy, mice were transferred to clean containers equipped with clean water bottles, both of which had been sterilized by steam. Traps and DDT in runways were used to destroy mice that escaped while treatment was in progress and also to prevent reintroduction of *L. ballum* by the common house mouse. (Author's summary)

281. TOTTON, M. Ringtail in new-born Norway rats. A study of the effect of environmental temperature and humidity on incidence. *J. Hyg.* 56: 190–6 (June), 1958.

Ringtail in infant rats is shown to depend on humidity over a wide temperature range. It is not due to infection or diet, but probably to chronic cooling by evaporation, convection and conduction. Rats should either be bred in cages with solid floors, or else be given environmental conditions resembling those in the natural nest, which keep the young at a low saturation deficit during the early postnatal period. (Condensed from author's summary)

282. VOGE, M. Helminth infections in small laboratory mammals and methods of obtaining a helminth-free colony. *Proc. Animal Care Panel* 8: 107–12 (Sept.), 1958.

The most common cestodes and nematodes in rats, mice and guinea pigs are discussed and directions are given for the establishment of helminth-free animal colonies.

283. VOGEL, R. A. AND PADULA, J. F. Indirect staining reaction with fluorescent antibody for detection of antibodies to pathogenic fungi. *Proc. Soc. Exptl. Biol. Med.* 98: 135–9 (May), 1958.

The reaction of pathogenic fungi with human antisera and rabbit antihuman gamma globulin labeled with fluorescein is described. In at least one disease, cryptococcosis, preliminary evidence suggested that this indirect fluorescent-antibody technique may be superior to standard serologic tests.

XUM

284. WEBSTER, G. A. A report on *Toxocara canis*, Werner, 1782. *Can. J. Comp. Med.* 22: 272–9 (Aug.), 1958.

The life history of *Toxocara canis* is described. After ingestion by the dog of ova containing 2nd stage larvae, the larvae hatch out in the small intestine, invade the lymph vessels, travel to the liver and from there to the heart and lungs. The tissues along the migration route are severely damaged. Intrauterine infection is possible either by ingestion of infective ova during gestation or through reactivation of larvae encapsulated in the somatic tissues. At present no adequate control measures for this disease exist. A system of mandatory worming imposed on dog breeders and kennel owners and routine fecal examinations are recommended.

285. WEINER, D. Toxoplasmosis in animals. *J. Am. Vet. Med. Assoc.* 133: 546–50 (Dec. 1), 1958.

The clinical and pathological course of toxoplasmosis in cattle, sheep, dogs, cats and poultry is described. The epidemiology, diagnosis and chemotherapy of this parasitic disease is discussed.

286. WEXLER, B. C. AND MILLER, B. F. Severe arteriosclerosis and other diseases in the rat produced by corticotrophin. *Science* 127: 590–1 (Mar. 14), 1958.

Discarded Sprague-Dawley breeding rats, about 1 yr. old, were injected s.c. with corticotrophin (ACTH) in a dosage of 0.333 of a unit/100 gm body weight, 3 times/wk. for up to 7 wk. Necropsy findings revealed severe arteriosclerosis in the females but not in the males. However, the males showed polyarteritis nodosa, gastric ulcers, testicular atrophy and renal calculi. Stressful situations other than administration of ACTH, such as repeated pregnancy, also induced arteriosclerosis. In both male and female rats rapid aging was noted.

287. WICHMANN, R. W. AND VINCENT, D. J. Cnemidocoptic mange in the budgerigar (*Melopsittacus undulatus*). *J. Am. Vet. Med. Assoc.* 133: 522–4 (Nov. 15), 1958.

Current information on cnemidocoptic mange in the budgerigar as caused by *Cnemidocoptes pilae* is presented. Observations on the effect of several drugs in the treatment of the disease are described and their efficacy discussed. Recommendations for the treatment and control of this disease are discussed. (Condensed from author's summary)

288. WICKERT, W. A., ROSEN, S., DAWSON, H. A. AND HUNT, H. R. *Brucella bronchiseptica* vaccine for rats. *J. Am. Vet. Med. Assoc.* 133: 363–4 (Oct. 1), 1958.

A vaccine for *Brucella bronchiseptica* in rats has been prepared and tested. A colony has been protected against this enzootic disease by giving 3 inoculations to young rats. (Author's summary)

289. WIGAND, R. *Morphologische, biologische und serologische Eigenschaften der Bartonellen.* (*Morphological, Biological and Serological Properties of* Bartonellae.) Stuttgart, Thieme, 1958, 95 pp.

The species studied were *Haemobartonella muris, Eperythrozoon coccoides, H. muris musculi* and *Bartonella bacilliformis*. After an illustrated description of the morphology there are accounts of infection of laboratory animals and of serological tests, including the complement fixation test for *H. muris* and *E. coccoides*. (Condensed from *Vet. Bull.* 29: Abstr. No. 3009, 1959)

290. YOST, D. H. *Encephalitozoon* infection in laboratory animals. *J. Natl. Cancer Inst.* 20: 957–63 (May), 1958.

Encephalitozoon cuniculi infection in laboratory animals is a mild, febrile disease. The disease is seen in rabbits, mice, guinea pigs, rats, and, occasionally, dogs. The organisms are usually observed in the epithelial cells of the papillae of the kidney and in the urine of infected animals and are noted in and isolated from the granulomatous lesions in the brain. *Encephalitozoon* infection may be distinguished from toxoplasmosis by the degree of illness, the morphology of the organisms, selected staining techniques, and characteristic lesions.

291. AINSWORTH, G. C. AND AUSTWICK, P. K. C. *Fungal Diseases of Animals.* Farnham Royal, Bucks, England, Commonwealth Agricultural Bureaux (*Rev. Ser.* No. 6), 1959, 148 pp.

A review of the literature, to the end of 1957, of the fungi associated with disease in numerous species of animals (cat, dog, goat, guinea pig, hamster, horse, monkey, mouse, rabbit, rat, sheep, pig, cattle, fowl, mink, opossum) is presented. The book contains the following chapters: Aspergillosis; moniliasis; cryptococcosis; epizootic lymphangitis; sporotrichosis; histoplasmosis; North American blastomycosis; coccidioidomycosis; haplomycosis; rhinosporidiosis; mucormycosis; bovine mycotic abortion; mycotic mastitis; diseases caused by actinomycetes: actinomycosis, nocardiosis, streptothricosis, mycotic dermatitis and strawberry foot rot; ringworm; mould toxicoses and poisonous fungi; ergotism. Synonyms of the name of the disease, the pathogen, hosts and geographic distribution are given for each disease. A detailed bibliography is included.

292. BAKER, J. A. Assuring distemper immunity. *Pure-Bred Dogs-Am. Kennel Gaz.* Jan., 1959, 4 pp.

Methods are presented for detection of immunity against canine distemper, infectious canine hepatitis and *Leptospira canicola, L. pomona* and *L. icterohemorrhagiae*. Quantity of distemper antibodies also can be determined for application of a nomograph which predicts the age to vaccinate puppies before they are whelped. Other applications of the serological service are discussed.

293. BAKER, J. A., ROBSON, D. S., GILLESPIE, J. H., BURGHER, J. A. AND DOUGHTY, M. F. A nomograph that predicts the age to vaccinate puppies against distemper. *Cornell Vet.* 49: 158–67 (Jan.), 1959.

A nomograph relating the serum titer of the mother to the age at which her progeny will respond to vaccination is presented for routine clinical application. The nomograph was field-tested with success on 57 dogs from 13 litters in which the age of vaccination ranged from 4 to 12 wk., and a statistical analysis indicated that use of the nomograph will result in a rate of at least 95% vaccination success. This procedure could supplant the practice of giving antiserum for temporary protection of young puppies. (Condensed from author's summary)

294. BARRON, C. N. AND SAUNDERS, L. Z. Intraocular tumors in animals. II. Primary nonpigmented intraocular tumors. *Cancer Research* 19: 1171–4 (Dec.), 1959.

A review of the literature on primary nonpigmented intraocular tumors in animals yielded 8 reports of retinoblastomas of which the authors describe 3. *Case 1* is a hemangioma of the iris of a dog, which is described in detail. *Case 2* is chondrosarcoma of the globe in a 2½-yr.-old cat, which has not been previously reported in an intraocular site. *Case 3* is a leiomyosarcoma of the iris and ciliary body in a dog, the only prior report of which has been in a woman. (18 references and 14 figs.)

295. BELL, J. F. Transmission of rabies to laboratory animals by bite of a naturally infected bat. *Science* 129: 1490–1 (May 29), 1959.

An insectivorous bat that attacked a man in western Montana was induced to bite suckling mice. Subsequently the bat died, and brain and salivary gland suspensions were inoculated into other mice. Rabies virus was isolated from all 3 groups of mice. It has yet to be demonstrated that insectivorous bats can become true carriers of infection that is infective but symptom-free. (Author's summary modified)

296. BENJAMIN, M. M. AND LUMB, W. V. *Haemobartonella canis* infection in a dog. *J. Am. Vet. Med. Assoc.* 135: 388–90 (Oct. 1), 1959.

After removal of the spleen containing a hemangioma, a severe anemia developed in a dog. In stained smears of the blood, organisms having the morphological characteristics of *Haemobartonella canis* were demonstrated in the erythrocytes. Transmission of the infection to 2 experimentally splenectomized dogs produced an anemia. Demonstration of characteristic organisms in their blood resulted in the diagnosis of haemobartonellosis. (Author's summary)

297. BEVERLEY, J. K. A. Congenital transmission of toxoplasmosis through successive generations of mice. *Nature* 183: 1348–9 (May 9), 1959.

Swiss mice were infected with a strain of *Toxoplasma* by s.c. inoculation (6 between the 8th–16th day of pregnancy, one 2 days after mating and one 5 days after delivery). All 8 mice transmitted the infection to some of the 2nd generation, 4 continued to the 3rd generation and 1 through the 4th and 5th generations. Infection seems to be transmitted before birth or by the milk, but not by droplet, feces, urine or copulation. Natural infection is almost unknown; adult mice can be infected naturally only by cannibalism.

298. BIESTER, H. E. AND SCHWARTE, L. H. *Diseases of Poultry*. 4th ed. Ames, Iowa State University Press, 1959, 1103 pp.

The book deals with the following topics: Anatomy; digestion; genetics as related to pathology; hematology; disease prevention; feeding and vitamins; pullorum disease; paratyphoid and paracolon infections; typhoid; cholera; tuberculosis; infectious coryza and chronic respiratory disease; brucellosis, anthrax, pseudotuberculosis, tetanus, hepatitis; listeriosis, botulism, erysipelas, goose influenza; streptococcosis, staphylococcosis, arthritis, coli granuloma and colibacillosis; fungal diseases; leukosis complex; infectious bronchitis and laryngotracheitis; Newcastle disease; ornithosis; encephalomyelitis; pox; plague; synovitis; rabies; monocytosis; neoplasms; parasites; nematodes, acanthocephalids; cestodes; trematodes; protozoa; surgery; vicious habits; poisons and toxins.

299. BJERKEDAL, T. AND PALMER, C. E. Competing forces of mortality in long-term animal experiments. Observation on the interaction between experimental tuberculosis and extraneous forces. *Am. J. Hyg.* 70: 246–53 (Nov.), 1959.

The role of extraneous forces, as expressed in mortality, is discussed in long-term animal experiments, as illustrated by results from experimental studies of tuberculous infection in guinea pigs. The extraneous forces apparently do not act independently of the experimentally induced tuberculous infection. During the early period after challenge with virulent tubercle bacilli, the mortality rates for several of the challenged groups appear to be significantly lower than for the normal control groups. This suggests that the tuberculous infection, before progressing to the point of causing death, provides some degree of protection against the extraneous forces to which normal control animals succumb.

300. BRIODY, B. A. Response of mice to ectromelia and vaccinia viruses. *Bacteriol. Revs.* 23: 61–95 (June), 1959.

Spontaneous infection with ectromelia virus may occur by contact with ectromelia virus or with mice infected with this virus. Latent ectromelia was not found to be responsible for any occurrence of mouse pox. An important factor in the epizootic pattern of the disease is the presence of a genetically susceptible population of mice. Ectromelia is diagnosed by the hemagglutination-inhibition test which can be carried out quickly and conveniently with 0.05 ml of serum. Effective control of the disease is possible by vaccination.

301. BURNET, F. M. AND STANLEY, W. M., ed. *The Viruses*. Vol. 3. *Animal Viruses*. 1st ed. New York, Academic Press, 1959, 428 pp.

302. CARLSON, L. D. AND JACKSON, B. J. The combined effects of ionizing radiation and high temperature on the longevity of the white rat. *U.S. Air Force School of Aviation Medicine Rept.* 58–156: 1–8 (Mar.), 1959.

Male Sprague-Dawley rats, individually caged, were exposed to irradiation from a Co^{60} source for 16 hr/day for a period lasting from 4 to 16 mo. of age. One group was kept at 28° ± 1°C, the other at 35° ± 1°C. The days of age at which 50% were dead (ET_{50}) were determined and discussed. Controls kept at 26° had an ET_{50} of 445 days.

303. CELLO, R. M., MOULTON, J. E. AND MCFARLAND, S. The occurrence of inclusion bodies in the circulating neutrophils of dogs with canine distemper. *Cornell Vet.* 49: 127–46, 1959.

Blood smears prepared from 16 dogs showing clinical signs of distemper showed intracytoplasmic inclusion bodies in the neutrophils when stained with Schorr's stain. By means of fluorescent-antibody studies the inclusions were shown to contain specific viral antigen of distemper disease.

304. CHENG, D. W. Effect of progesterone and estrone on the incidence of congenital malformations due to maternal vitamin E deficiency. *Endocrinology* 64: 270–5 (Feb.), 1959.

The subcutaneous administration of progesterone or estrone at certain levels continuously or by a single dose either reduced or abolished the incidence of congenital malformations in Holtzman rats with maternal avitaminosis E. (From author's summary)

305. CHRISTIAN, J. J. Lack of correlation between adrenal weight and injury in grouped male albino mice. *Proc. Soc. Exptl. Biol. Med.* 101: 166–8 (May), 1959.

Albino male mice from the Naval Medical Research Institute colony were used. Amount of scarring due to injury from fighting was compared in 280 mice from 50 populations of 4, 5 or 6 mice each. No relationship was found between adrenal weight and absence or presence of scarring. It was concluded that adrenal hypertrophy after 1 wk. of grouping did not reflect amount of injury received.

306. CLARKSON, T. B., PRICHARD, R. W., NETSKY, M. G. AND LOFLAND, H. B. Atherosclerosis in pigeons. Its spontaneous occurrence and resemblance to human atherosclerosis. *A.M.A. Arch. Pathol.* 68: 143–7 (Aug.), 1959.

Pigeons of the Autosexing King, Silver King, and White Carneau breeds have spontaneous atherosclerosis closely resembling the

human disease, grossly and microscopically. Pigeons of different breeds, the Show Racer and Racing Homer, have almost no atherosclerosis. The evidence suggests that atherosclerosis in the pigeon is not related to sex, diet, or exercise but rather to a genetic factor and age. (Author's summary)

307. COMAR, C. L. Radiation biology in veterinary education and research. *J. Am. Vet. Med. Assoc.* 134: 162–5 (Feb. 15), 1959.

The following diagnostic tests for laboratory animals are described: *1)* thyroid function, by the uptake of radioactive iodine by the thyroid gland; *2)* kidney function, by administering a labeled radiopaque material (Diodrast) and measuring radioactivity over the kidney; *3)* cardiac output, by the dye dilution iechnique; *4)* liver function, by using rose bengal dye with labeled todine; *5)* blood and plasma volume by means of radioiodinated serum albumin; *6)* pernicious anemia, by the intrinsic factor.

308. COVAULT, C. H. AND SLOSS, M. W. Dithiazanine therapy in strongyloidiasis. *Gaines Dog Research Progr.*, Winter 1958–59, pp. 1–3.

The therapeutic efficacy of dithiazanine in strongyloidiasis of dogs is pointed out. The drug is administered in capsules and no sign of toxicity or discomfort has been observed in treated animals. The question is discussed how many negative tests over how long a period of time are required before an animal can be considered to be cured.

309. DOLAN, M. M. AND FENDRICK, A. J. Incidence of *Trichophyton mentagrophytes* infections in laboratory rats. *Proc. Animal Care Panel* 9: 161–4 (Dec.), 1959.

Evidence is shown that the occurrence of ringworm in rats is influenced by breeding and care and handling practices. The "carrier" state of unapparent infection may emerge to overt infection under suitable environmental conditions of temperature and humidity.

310. DOLOWY, W. C. Repair of prolapsed rectums in mice. *J. Am. Vet. Med. Assoc.* 135: 605 (Dec. 15), 1959.

When 6 adult female albino mice developed prolapsed rectums spontaneously, they were subjected to ether-alcohol inhalation anesthesia, held in a nose-down vertical position, and the rectums replaced. One mouse died during the night; the other 5 were alive 1 mo. later. The sutures had not been removed and prolapse had not returned.

311. DOMÉNICO, A. D. AND ANDREOTTI, H. T. Mechanism of splenic protection against '*Bartonella muris*' in the parabiotic rat. *Am. J. Physiol.* 197: 795–8 (Oct.), 1959.

Splenectomized albino rats, carriers of *Bartonella muris*, develop a hemolytic syndrome in about 3–4 days after operation. If the splenectomized animal is attached to a normal partner in true parabiosis, for example with cross circulation, the normal partner protects the other. If it is attached to a normal partner in false parabiosis, for example without cross circulation there is no protection. The difference in the behavior of these two types of union is associated with the different interchange of blood cells: about 0% in false and about 50% in true parabionts and not with the interchange of humors whose difference is not statistically significant. It is concluded that the splenic protection is local and not mediated through a humoral substance. (Author's summary)

312. DOW, C., JARRETT, W. F. H., JENNINGS, F. W., MCINTYRE, W. I. M. AND MULLIGAN, W. The production of active immunity against the canine hookworm *Uncinaria stenocephala*. *J. Am. Vet. Med. Assoc.* 135: 407–11 (Oct. 15), 1959.

Pups were immunized against hookworm infections by vaccinating them with irradiated infective larvae. This is significant with respect to practical vaccination measures and to fundamental immunity problems in parasitic diseases. (Author's summary)

313. DUNLAP, J. S., DICKSON, W. M. AND JOHNSON, V. L. Ionographic studies of rabbits infected with *Eimeria stiedae*. *Am. J. Vet. Research* 20: 589–91 (May), 1959.

The degree of liver damage in sublethal liver coccidiosis of crossbred New Zealand white rabbits was studied. Protein and lipoprotein fractions of serum were analyzed using ionography (paper electrophoresis).

314. DUPONT, J. R., HUGGINS, R. A., DEAVERS, S. AND SMITH, E. L. Effects of certain anesthetics on distribution of red cells in the dog. *Am. J. Physiol.* 197: 978–80 (Nov.), 1959.

A total of 28 dogs were anesthetized using either morphine, pentobarbital or a combination of the two, and the red cell and plasma volume were determined before and 2 wk. after splenectomy. As controls, previously obtained data for 60 unsplenectomized dogs anesthetized with morphine-pentobarbital were used. The results are tabulated.

315. FARID, Z. AND BARCLAY, W. R. Histoplasmosis. *In vivo* studies in the rabbit ear chamber. *A.M.A. Arch. Pathol.* 68: 413–8 (Oct.), 1959.

The course of *Histoplasma capsulatum* infection in living tissue and the difference in the tissue reactions to primary and to secondary histoplasmosis was studied by means of the rabbit ear chamber technique. Primary infection was found to be progressive and immunity developed too late to limit extensive tissue destruction at the inoculation site. In reinfection histoplasmosis, the inflammatory response was immediate and intense with localized tissue destruction but restriction of the spread of infection.

316. FERREIRA-NETO, J. M. The value of some liver function tests in dogs. Thesis, Cornell, 1959, 69 pp.

The comparative efficiency of the following liver function tests in dogs was studied: Bromsulphalein retention test, Bromsulphalein clearance, serum uric acid content, Takata Ara reaction, and serum cholinesterase. A review of the literature on these tests with 65 references is presented. On the basis of experiments with 20 dogs the following conclusions were drawn: the application of Bromsulphalein clearance did not appear to be practical. The Bromsulphalein test and uric acid determination were the most reliable liver tests used in this work. The Takata Ara reaction was weakly positive in only 50% of the cases with liver lesions but was helpful in the diagnosis of chronic conditions. Cholinesterase activity as measured by Caraway's method ranged from 26–69 units in normal dogs and varied in liver disease.

317. FISHLER, J. J. Cat diseases preventable. Abstract of paper presented at Symposium on Health of Small Animals, Chicago, July 1959. *J. Am. Vet. Med. Assoc.* 135: 522 (Nov. 15), 1959.

Enteritis and pneumonitis in cats can be prevented by sanitation (scrubbing) and use of Cl solutions as disinfectants. Cats should be isolated from one another and vaccinated in advance of possible exposure.

318. FLYNN, R. J. Follicular acariasis of mice caused by *Psorergates simplex* successfully treated with Aramite. *Am. J. Vet. Research* 20: 198–200 (Jan.), 1959.

Experiments with female CF No. 1 mice, 9–13 mo. old, showed that an aqueous suspension of Aramite (2-*p*-tertbutylphenoxy isopropyl-2-chloroethyl sulfite) combined with a wetting agent is completely effective against follicular acariasis of mice caused by *Psorergates simplex*. The use of mice infested with *P. simplex* as test animals for the screening of compounds for topical and systemic acaricidal activity is suggested.

319. FLYNN, R. J. Studies on the etiology of ringtail of rats. *Proc. Animal Care Panel* 9: 155–60 (Dec.), 1959.

The incidence and severity of experimentally produced ringtail in rats was found to vary with certain factors in the environment. Under all combinations of conditions, maximum incidence occurred at about 1 wk. of age. When steel cages were used the incidence of ringtail in Sprague-Dawley rats fed an unsupplemented Rockland Mouse Diet, was inversely proportional to the relative humidity. Dietary supplementation had little influence although the possibility that fats are involved in the etiology of ringtail was not ruled out. Under identical conditions Long-Evans and Sherman strains showed a much lower incidence than Wistar and Sprague-Dawley strains.

320. FLYNN, R. J. Demodectic and sarcoptic mange of dogs successfully treated with Aramite. *J. Am. Vet. Med. Assoc.* 134: 177–9 (Feb. 15), 1959.

When dogs infected with *Demodex canis* or *Sarcoptes scabiei* were treated by weekly bathing with a 2% aqueous suspension of a wettable powder containing 15% Aramite, improvement was noted in every case within 30 days and complete recovery occurred within 90 days.

321. GANDAL, C. P. AND SAUNDERS, L. Z. The surgery of subcutaneous tumors in parakeets (*Melopsittacus undulatus*). *J. Am. Vet. Med. Assoc.* 134: 212–8 (Mar. 1), 1959.

A series of 45 external growths in parakeets was studied. Anesthesia by intramuscular injection of Equithesin (combination of chloral hydrate, pentobarbital and Mg sulfate) and operative technique are discussed.

322. GENTLES, J. C., BARNES, M. J. AND FANTES, K. H. Presence of griseofulvin in hair of guinea pigs after oral administration. *Nature* 183: 256–7 (Jan. 24), 1959.

Bulked hair from guinea pigs treated with 23 consecutive daily oral doses of 30–40 mg/kg of griseofulvin was found to contain 5–6 μg griseofulvin/gm of hair.

323. GOLDBERG, H. C., ARLEIN, M. S., KAPLAN, S., DEVINE, J. J. AND KINDLER, J. Procedure for the physician and veterinarian in dealing with ringworm of the scalp. *J. Am. Vet. Med. Assoc.* 135: 332–3 (Sept. 15), 1959.

Among the 3 types of tinea capitis only the type caused by *Microsporum canis* is readily transmitted from infected animals (usually dogs and cats) to man. Diagnostic tests and protective measures are discussed.

324. GROSS, P., WESTRICK, M. L. AND MCNERNEY, J. M. The pulmonary response to certain chronic irritants. (An experimental study on rats and guinea pigs.) *A.M.A. Arch. Pathol.* 68: 252–61 (Sept.), 1959.

Rats and guinea pigs were subjected to intratracheal injection of aviruient tubercle bacilli, of cholesterol alone or adsorbed to kaolin, of corn oil, serum or egg albumin adsorbed to clay or asbestos, and of dusts from feldspar, limestone, kaolin, colloidal silica, asbestos, vitreous Al silicate and Ca silicates. The lung sections of these experimental animals and of disease-free controls were examined. The interrelationship of the perivascular cells and the reticulin framework was studied.

325. HABERMANN, R. T. Spontaneous diseases and their control in laboratory animals. *Public Health Repts. (U.S.)* 74: 165–9 (Feb.), 1959.

Diseases in laboratory animals (cat, guinea pig, hamster, mouse, rat, rabbit), caused by internal or external parasites, bacteria or viruses, and their treatment and control are discussed. Salmonellosis, digestive and chronic respiratory diseases are reviewed in detail.

326. HAGEN, K. W., JR. Chronic respiratory infection in the domestic rabbit. *Proc. Animal Care Panel* 9: 55–60 (June), 1959.

Out of 857 young rabbits produced by 45 white New Zealand does, a total of 35 young and 5 mature does developed symptoms of respiratory infection and died within 2–7 days. *Pasteurella multocida* was the predominating organism isolated from the respiratory tract, although *Alcaligenes bronchiseptica* and *Micrococcus pyogenes* were also found. Experimental studies suggest that natural transmission via the respiratory route from mother to offspring takes place within a few days after birth. The results of treatment with sulfaquinoxaline and furazolidone are discussed. (Also published in *J. Am. Vet. Med. Assoc.* 133: 77–80 (July), 1958, "Enzootic Pasteurellosis in domestic rabbits. I. Pathology and bacteriology.")

327. HERRLEIN, H. G. Elimination of oxyurids from the laboratory mouse. *Proc. Animal Care Panel* 9: 165–6 (Dec.), 1959.

In the elimination of oxyurids from mice, piperazine therapy is more effective than phenothiazine therapy. For best results the piperazine is started on young adult mice prior to breeding exposure, and is continued at 6-wk. intervals. A solution of 7 parts/1000 of piperazine hexahydrate in tap water is fed to breeding mice and their young for 3 consecutive days.

328. HERRMANN, E. C., JR., ENGLE, C. AND PERLMAN, P. L. Action of anti-inflammatory agents on endotoxin-induced lung inflammation in mice. *Am. J. Physiol.* 197: 803–7 (Oct.), 1959.

The instillation of *Escherichia coli* endotoxin (lipopolysaccharide) intranasally into mice produced severe lung lesions and a substantial increase in lung weight. The extent of lung inflammation was evaluated either by weighing the lungs or by assigning a score to each lung depending on the extent of liver-colored lesions. (From author's summary)

329. HOERLEIN, B. F. Clinical spinal radiography in the dog. *J. Am. Vet. Med. Assoc.* 134: 343–8 (Apr. 15), 1959.

The importance of spinal radiography is demonstrated. Techniques for spinal radiography and diseases which may be diagnosed by its application are described.

330. HOSKINS, H. P., LACROIX, J. V. AND MAYER, K., ed. *Canine Medicine. A Text and Reference Work.* 2nd ed., Santa Barbara, Calif., Am. Veterinary, 1959, 854 pp.

The clinical examination; administration of medicine; nutrition; diseases of the alimentary tract; respiratory system; urogenital system; blood and blood-forming organs; heart; endocrine glands; anatomy of the skin; locomotor system; ear; eye; nervous system; allergies; metazoan infections; mycotic diseases; rickettsial diseases; spirochetal diseases; bacterial diseases; viral diseases; diseases caused by physical and toxic agents; pediatrics; geriatrics; euthanasia, inhalation therapy; parenteral fluid therapy appear.

331. HUNDEMANN, A. S. AND HOLBROOK, A. A. A practical method for the decontamination of microbiologic laboratories by the use of formaldehyde gas. *J. Am. Vet. Med. Assoc.* 135: 549–53 (Dec.), 1959.

Formaldehyde gas combined with a high percentage of humidity was shown to be an economical and efficient method of fumigation for a laboratory where surface decontamination is of primary importance. Various amounts of 10^3 dilutions of Newcastle disease virus and vesicular stomatitis virus, cultures of *Erysipelothrix rhusiopathiae*, a mixed culture of bacteria and mold isolated from grass, and cultures of airborne contaminants were all completely inactivated when exposed to the fumigation procedures in open Petri dishes. When various dilutions of the viruses were exposed to the gas in open tubes or tubes closed with cotton plugs, the titers of both viruses decreased, but the viruses were not completely inactivated because gas was unable to penetrate the depth of the suspending medium. (Author's summary)

332. JONES, L. P. Purulent panophthalmitis in laboratory rats. *J. Am. Vet. Med. Assoc.* 135: 502–3 (Nov. 15), 1959.

A strain of *Staphylococcus aureus* was isolated from rats affected with acute purulent panophthalmitis. The infection involved the older, more mature animals and was confined to the region of the eye. The rats were effectively treated with chlortetracycline (both oral and local application) and recovery was hastened with a 2-mg-intramuscular dose of prednisolone. (Author's summary)

333. KAMPSCHMIDT, R. F. AND MCCOY, T. A. Carcass weight changes in rats bearing Walker carcinosarcoma 256. *Proc. Soc. Exptl. Biol. Med.* 101: 507–9 (July), 1959.

Liver weights of Holtzman rats bearing 40–60 gm Walker carcinosarcoma 256 tumors were directly correlated with changes in carcass weight of host. Removal of 70% of liver during rapid growth of tumor resulted in a gain in carcass weight without affecting growth of the tumor. (Author's summary)

334. KAPLAN, W. AND AJELLO, L. Oral treatment of spontaneous ringworm in cats with griseofulvin *J. Am. Vet. Med. Assoc.* 135: 253–61 (Sept. 1), 1959.

Twenty-two cats with *Microsporum canis* ringworm were treated with orally administered griseofulvin. Of the 18 animals that showed visible lesions prior to therapy, 10 were clinically normal within 3 wk., 6 at the end of 1 month, and 2 at the end of 5 weeks. During the course of the study, 8 cats were rendered culturally negative through the use of this drug alone. The toxicity of griseofulvin for cats appears to be low. Of the 22 cats, only 1 developed a possible side reaction. This animal had a generalized pruritus after 3 wk. of daily therapy which disappeared spontaneously in 3 days without interruption of treatment. (From author's summary)

335. KEENEY, E. L. AND HUPPERT, M. Immunization against superficial fungous infection. I. Studies on experimental animals. *J. Invest. Dermatol.* 32: 7–13 (Jan.), 1959.

A technique for preparing sterile antigenic material from broth cultures of one strain of *Trichophyton mentagrophytes* is described. The procedure used was designed to destroy the fungus while extracting the antigen in as nearly its native state as possible. Guinea pigs treated with this antigen by topical application developed a hypersensitivity and an increased resistance to infection with homologous fungus.

336. KEPLINGER, M. L., LANIER, G. E. AND DEICHMANN, W. B. Effects of environmental temperature on the acute toxicity of a number of compounds in rats. *Toxicol. Appl. Pharmacol.* 1: 156–61 (Mar.), 1959.

The acute intraperitoneal toxicity of each of 58 compounds was determined in adult albino rats of Sprague-Dawley stock, exposed to 3 different environmental temperatures: 8°, 26° and 36°C. Except for strychnine, chlorpromazine and promazine, all compounds were most toxic at 36°C, while promazine and chlorpromazine were most toxic at 8°C. (Author's summary)

337. KRESHOVER, S. J. Congenital dental defects. *J. Dental Med.* 14: 41–8 (Jan.), 1959.

It is shown that the developing dental tissues of young *in utero* may be significantly affected by maternal disease. However, a defect of development can only involve the organs or tissue sites that are incompletely formed at the time of maternal disturbance. Certain injurious agents may also have a selective effect on specific tissues. The information of this report may aid in further evaluation of the placenta as a barrier to or pathway for transfer of certain injurious agents from mother to fetus.

338. KRISE, G. M. AND WALD, N. Hematological effects of acute and chronic experimental blood loss in the *Macaca mulatta* monkey. *Am. J. Vet. Research* 20: 1081–5 (Nov.), 1959.

Thirty normal male *Macaca mulatta* monkeys, 1.8–3.6 kg wt., were subjected to acute (37% of blood volume) or chronic (2.5%–24% of blood volume/wk. over 8 wk) blood loss, respectively. In animals undergoing severe acute blood loss the erythroid elements of the peripheral blood returned to normal within 28 days. Chronic experimental blood loss of 2.5%–6% of the blood volume did not alter significantly the peripheral erythroid elements whereas higher losses could not be compensated for during the 8-wk. period.

339. KULLANDER, S. On the occurrence and morphology of spontaneous tumours in the pituitary, adrenals, gonads and mammary glands in rats before and after gonadectomy, irradiation and treatment with oestrogen or progesterone. *Brit. J. Cancer* 13: 497–505 (Sept.), 1959.

Analysis was made of the frequency and morphology of spontaneous tumors in the pituitary, adrenals, gonads and mammary glands of a closed colony of rats, consisting of normal females and males, animals gonadectomized at age of 3 wk., normal and spayed females exposed to x-ray irradiation of the whole body and spayed females treated with estrogen or progesterone.

340. LIPSCHUTZ, A., IGLESIAS, R., ROJAS, G. AND CERISOLA, H. Spontaneous tumourigenesis in aged guinea-pigs. *Brit. J. Cancer* 13: 486–96 (Sept.), 1959.

Necropsy results obtained on 25 guinea pigs, 4–6 yr. old, are reported. Tiny nodules of uterine adenocarcinoma may originate spontaneously in nonoperated guinea pigs, 4–6 yr. old. The tentative assumption is made that in aged guinea pigs there is a tumorigenic ovarian-hypophyseal imbalance which is genetically determined in the course of domestication or which is due to environmental influences. Facts strengthening this assumption are the occurrence of other tumors known to be dependent on hormonal homeostasis in the body (uterine and extrauterine leiomyoma, thyroid and suprarenal adenoma) and the presence of endometriosis, adenomatous polyps and of a pronounced cystic condition of the ovary as found in ovarian-hypophyseal imbalance.

341. LOMBARD, L. S. AND WITTE, E. J. Frequency and types of tumors in mammals and birds of the Philadelphia Zoological Garden. *Cancer Research* 19: 127–41 (Feb.), 1959.

The increase frequency of neoplasms seen in the period 1935–1955 was associated with an increased mean age in most captive

wild species and the increased longevity was attributed to better nutritional and environmental care. Other causative agents such as the increased distribution of carcinogens in the environment and diet of the animals must also be considered.

342. LUMB, W. V. Haemobartonellosis in the dog. *Gaines Dog Research Progress*, Winter 1958–1959, p. 6.

Haemobartonellosis in nonsplenectomized dogs assumes a latent form, while in splenectomized dogs it is either acute or chronic. Both forms are characterized by anemia. The natural mode of transmission has not been definitely established. The role of the spleen is rather peculiar in this disease.

343. MENGES, R. W. Control of leptospirosis in man and animals. *Public Health Repts. (U.S.)* 74: 149–52 (Feb.), 1959.

Control measures for leptospirosis in domestic, wild and laboratory animals are discussed.

344. MORGAN, H. C. A qualitative sulfobromophthalein sodium retention test of liver function in the horse. *J. Am. Vet. Med. Assoc.* 135: 412–16 (Oct. 15), 1959.

A standard solution of Bromsulphalein (BSP, 40 ml of a 5% solution) is given to all average-sized horses regardless of weight. Blood is withdrawn only once, that is, 15 min. after BSP injection. Heparin should be used for withdrawal. Results for normal horses and horses with liver diseases are tabulated.

345. MORRIS, M. L. Intranasal intubation. *Prescription Diets Bull.* 3, p. 1 (Sept.), 1959.

A method for the administration of electrolyte solutions in depleted feline by intranasal intubation is described. A topical anesthetic is instilled 3–4 min. prior to intubation. A ureteral catheter is then lubricated and inserted gently through the nasal passage into the esophagus. Liquid foods may be injected through the catheter using a 20–30-cc glass syringe.

346. MORRIS, M. L. Which diet shall I prescribe? Clinical indication index. *Prescription Diets Bull.* 3, p. 2 (Sept.), 1959.

Diets indicated for the most common diseases of dogs and cats are listed.

347. NATIONAL RESEARCH COUNCIL, COMMITTEE ON THE HANDBOOK OF BIOLOGICAL DATA. *Handbook of Toxicology*. Vol. 1: *Acute Toxicities of Solids, Liquids and Gases to Laboratory Animals*, edited by W. S. SPECTOR. Vol. 2: *Antibiotics*, edited by W. S. SPECTOR. Vol. 3: *Insecticides*, by W. O. NEGHERBON. Vol. 4: *Tranquilizers*, edited by R. M. GREBE. Vol. 5: *Fungicides*, edited by D. S. DITTMER. Philadelphia, Saunders, 1956–9.

348. NEWBERNE, J. W., BITTLE, J. L. AND MAYER, K. Clinical differentiation of feline viral diseases. *Allied Veterinarian* 30: 50–3 (Mar.–Apr.), 1959.

In feline panleukopenia the course is rapid and the mortality high, whereas in feline pneumonitis the course is prolonged and the mortality is generally low. These and other clinical differential characteristics are described. Available vaccines produce satisfactory immunity against these diseases. In addition, purely clinical evidence indicates that the feline pneumonitis vaccine may have some therapeutic effect. While feline pneumonitis is caused by a psittacoid viral agent, a number of immunologically different true viruses cause respiratory infections in cats which are clinically indistinguishable from pneumonitis. In some cases of clinical pneumonitis that were thoroughly studied, both feline pneumonitis virus and other respiratory viruses were found to be involved. Such dual infections tended to be more severe and sometimes showed a high mortality. There was some evidence that vaccine control of the pneumonitis virus reduced the severity of such mixed outbreaks. Feline pneumonitis can be distinguished histopathologically and immunologically from respiratory infections caused by other viruses. (Author's summary)

349. NEWTON, W. L., WEINSTEIN, P. P. AND JONES, M. F. A comparison of the development of some rat and mouse helminths in germfree and conventional guinea pigs. *Ann. N. Y. Acad. Sci.* 78, Art. 1: 290–306 (May), 1959.

The rat nematode *Nippostrongylus muris*, the mouse nematode *Nematospiroides dubius*, and the mouse tapeworm *Hymenolepis nana* were found to develop to apparently normal fertile adults in germfree guinea pigs, animals generally considered to be abnormal hosts for these parasites. While worm yields in the case of *N. muris* were very low, in the case of *N. dubius* they were as high as 23% of the larvae inoculated. Development of these helminths in conventional guinea pigs was either extremely poor or failed to occur. The significance of these findings is discussed. (Author's summary)

350. NOBLE, R. L. AND CUTTS, J. H. Mammary tumors of the rat: A review. *Cancer Research* 19: 1125–39 (Dec.), 1959.

The article is divided into the following sections: Origin and characteristics of spontaneous mammary tumors and of transplanted mammary tumors of spontaneous origin; mammary tumors induced by aminofluorene compounds, carcinogenic hydrocarbons or hormones; implication of a virus in rat mammary tumors; mammary tumor, host relationship; chemotherapeutic studies. (145 references)

351. ORKIN, M. AND SCHWARTZMAN, R. M. A comparative study of canine and human dermatology. II. Cutaneous tumors—the mast cell and canine mastocytoma. *J. Invest. Dermatol.* 32: 451–66 (Mar.), 1959.

Mast cell tumors were studied in 13 dogs by means of punch and excision biopsy and touch smears. Since there is a striking similarity between the canine mastocytoma and human urticaria pigmentosa, the canine mast cell tumor appears suitable for experimentation in relation to urticaria pigmentosa in man.

352. PHILLIPS, B. P. AND WOLFE, P. A. The use of germfree guinea pigs in studies on the microbial interrelationships in amoebiasis. *Ann. N. Y. Acad. Sci.* 78, Art. 1: 308–313 (May), 1959.

When 73 germfree guinea pigs were inoculated intracecally with *Endamoeba histolytica* and sacrificed after 1–58 days, none showed gross lesions at necropsy, and microscopic examination of the cecal tissue did not reveal amoebas in any of the layers. On the other hand, 41 out of 53 conventional guinea pigs inoculated with *E. histolytica* developed acute ulcerative lesions. Thus, intestinal amebiasis presents an example of the fact that microbial interrelationships can be involved essentially in the etiology of enteric disease.

353. POOL, W. A., ed. *The Veterinary Annual. First Year.* Baltimore, Williams & Wilkins, 1959, 363 pp.

Veterinary work in the United States and in Denmark, Sweden, Canada, Australia, New Zealand, South Africa and Britain is dis-

XUM

cussed in separate articles. The current literature on diseases (bacterial, fungal, protozoan, viral, parasitic, nutritional, tumors, reproductive system (including a review of artificial insemination)), poisonings, radiation, radiology, blood groups, pharmacology, veterinary surgery, euthenasia, legal matters and technique is reviewed. Recent pharmaceutical and dietetic preparations, medical appliances and new publications are listed.

354. RAY, A. AND SADHU, D. P. Oxidative processes in hypervitaminosis A in albino rats. *Am. J. Physiol.* 196: 1274–6 (June), 1959.

The effect of hypervitaminosis A on food consumption, gain of body weight and basal metabolism was studied. It was concluded that hypervitaminosis A inhibits liver respiration by affecting the dehydrogenase, or any immediate step following it, and the cytochrome *c*-cytochrome oxidase end of the succinoxidase system is little affected.

355. REBER, E. F., MALHOTRA, W. P., KREIER, J. P., NORTON, H. W. AND BEAMER, P. D. The effects of feeding irradiated flour to dogs. I. Growth. *Toxicol. Appl. Pharmacol.* 1: 55–60 (Jan.), 1959.

Beagle dogs, 14–38 wk. old, were fed for 24 wk. a complete ration in which nonirradiated or irradiated flour constituted 35% of the total solids. No statistically significant difference resulted in weight gained or feed consumed and there was no apparent effect on hemoglobin, red or white or differential white blood cell counts in the 2 groups.

356. REYNIERS, J. A. AND SACKSTEDER, M. R. Tumorigenesis and the germfree chicken: A preliminary report. *Ann. N. Y. Acad. Sci.* 78, Art. 1: 328–53 (May), 1959.

Tumors will develop in germfree chickens following an injection of Rous sarcoma UF filtrate or by a single injection of MCA/Bz into the right breast muscle. These tumors can be transmitted to other germfree and to conventional chickens. Tumors caused in conventional chickens by MCA/Bz cannot be passed on to other conventional chickens. However, such a transmission can be effected if the chickens are fed on antibiotics from hatching time.

357. RICHARDSON, F. L. AND HUMMEL, K. P. Mammary tumors and mammary-gland development in virgin mice of strains C3H, RIII, and their F_1 hybrids. *J. Natl. Cancer Inst.* 23: 91–107 (July), 1959.

The incidence of mammary tumors was high in virgin females of strain C3H and in reciprocal F_1 hybrids between strains C3H and RIII, but comparatively low in virgin females of strain RIII. The mean tumor age in the (C3H x RIII)F_1 virgin hybrids was less than in either parental strain but more closely resembled that of C3H. The mean tumor age in the (RIII x C3H)F_1 virgin hybrids was greater than that in strain C3H and not significantly different from that in strain RIII mice. The differences in incidence of mammary tumors and in mean tumor age between the 2 hybrid groups suggest that the agent in the milk of strains C3H and RIII differs in quality or quantity, that of C3H being the more active. (Condensed from author's summary)

358. RIGDON, R. H. Cataracts in parent chickens and first and second generation. *Federation Proc.* 18: Abstr. No. 1978 (Mar.), 1959.

A spontaneous cataract was found in 1 eye of a White Leghorn hen in 1955. She was mated with a male considered to be normal. Seven chicks from this mating developed cataracts. Cataracts have now occurred in chickens in the 2nd generation. These cataracts are associated with an iritis. The etiological agent apparently is the virus of lymphomatosis. In addition to the iritis and cataracts occurring in this group of chickens, some of the birds have developed tumors, splenomegaly, hepatomegaly and meningo-encephalomyelitis. The degeneration within the lens has been studied histologically and will be reported.

359. ROTHSTEIN, N. Vital staining of blood parasites with acridine orange. *J. Parasitol.* 44: 588–95 (Dec.), 1959.

Vital staining of the cellular elements of normal and parasitized whole blood with basic fluorochrome acridine orange was shown to be a rapid technique for studying differentiated leukocytes and stained parasitized erythrocytes in the presence of unstained normal erythrocytes. Microfilariae, trypanosomes and toxoplasms have also been stained. (From author's summary)

360. RUCH, T. C. (With the editorial assistance of TERRY, M. W.) *Diseases of Laboratory Primates.* Philadelphia, Saunders, 1959, 600 pp.

The book contains the following 14 chapters: Diet and disease, including nutritional diseases; diseases of the mouth and teeth; diarrhea and dysentery caused by bacteria and viruses; intestinal protozoa; intestinal helminths, with a survey of helminthic diseases; tuberculosis; miscellaneous diseases of the abdomen and chest, including generalized diseases; blood parasites; cardiovascular diseases and blood dyscrasias; diseases of the central nervous system and sense organs; diseases of the endocrine, reproductive, and urinary systems; bone diseases; diseases of the skin; neoplasia.

361. SCRIMSHAW, N. S., TAYLOR, C. E. AND GORDON, J. E. Interactions of nutrition and infection. *Am. J. Med. Sci.* 237: 367–403 (Mar.), 1959.

Tables are provided concerning the effect of nutritional deficiencies on bacterial, viral, rickettsial, helminth, protozoal infections and the effects of dietary excess of certain nutrients on protozoal infections. The following hosts were dealt with: guinea pig, mouse, rat, pigeon, monkey, dog, chicken, rabbit, lamb.

362. SHELTON, G. C., MAGNER, J. M., AND SANTMYER, P. H. Sodium pentachlorophenate as an ovicide for controlling ascariasis in swine. *J. Am. Vet. Med. Assoc.* 135: 229–33 (Aug. 15), 1959.

The efficiency of controlling swine ascarids by application of Na pentachlorophenate to soil is demonstrated.

363. SMITH, G. R. The production in mice of active immunity against *Pasteurella haemolytica*. *J. Comp. Pathol. Therap.* 69: 116–24, 1959.

Active immunity to intraperitoneal challenge with *Pasteurella haemolytica* in mucin was produced in mice by i.p. or intravenous injection of living or formol-saline vaccine or subcutaneous injection of adjuvant vaccine. The presence of immune antibodies in the sera of vaccinated mice was proved by passive mouse protection tests. Under the conditions used, i.p. vaccination produced a higher level of protection than s.c. vaccination. However, no difference in protection was noted between i.p. and i.v. vaccination. Injections (i.p.) of mouse serum, normal saline or veronal-saline buffer, respectively, 5–6 hr. before i.p. challenge with *Past. haemolytica* in mucin increased resistance to lower levels of challenge, but this effect was obliterated by increasing the challenge dose.

364. SMITH, H. M. Minerals curb turtle diseases. Abstract of paper presented at Symposium on Health of Small Animals. Chicago, July 1959. *J. Am. Vet. Med. Assoc.* 135: 39 (Nov. 15), 1959.

Mineral deficiency in turtles, causing shell softness and deformity, can be avoided by placing a ball of hard plaster of Paris in their aquaria. Common eye infections are reduced by a high concentration of Cu ions in the water which may be accomplished by adding small square pieces of Cu screen to the water.

365. TAYLOR, A. R., BRANDON, F. B. AND REYNIERS, J. A. Fractionation studies of tumor tissues from germfree chickens. *Ann. N. Y. Acad. Sci.* 78, Art. 1: 354–70 (May), 1959.

Tumor tissue was subjected to ultracentrifugal fractionation and electromicroscopic studies of the fractions. The electron micrographs are illustrated and discussed.

366. THOMPSON, S. W. The role of the United States Army medical nutrition laboratory's pathology branch in the study of irradiated foods. *J. Am. Vet. Med. Assoc.* 134: 387–91 (May 1), 1959.

Four generations of rats were maintained for 2 yr. on a composite control or irradiated diet. Histopathological studies of the 1st and 2nd generation completed to date did not reveal any significant differences in disease incidence between the 2 diet groups. Murine pneumonia occurred frequently in young rats and increased in severity in both groups with age. Chronic arteritis affected about 10% of the control and experimental rats. The number of rats fed the irradiated diet was too small to conclude whether the irradiated diet favored the incidence of tumors.

367. U.S. DEPARTMENT OF AGRICULTURE. Biochemical problems in determining the age of bruised animal tissue. *U.S. Dept. Agr. Farmer Coop. Serv. Rept.* 42, Feb., 1959, 36 pp.

Morphological and biochemical changes in bruised tissue of livestock were studied; a color test, using bilirubin, and a conductivity test are described for measuring the age of bruised tissue. The significance of various factors, including transportation, on bruising and healing of wounds is discussed.

368. WEBB, J. E., JR. AND SHEPHERD, E. L. Notes on control of mange mites in laboratory white mice with malathion. *J. Econ. Entomol.* 52: 790 (Aug.), 1959.

Malathion was compared with lindane for treating the bedding in a mite-infested laboratory colony of white mice to control *Myocoptes musculinus* (Koch) and *Myobia musculi* (Schrank). At the end of 1 wk. the mice in the lindane-treated jars were all either sick or dead while all mice—including the suckling young—in the malathion-treated jars were normal. When the adult, malathion-treated mice were killed, no mites were found either by scraping mange scabs or by examining washed and filtered residue under the dissecting microscope. The sprinkling of 0.5 ml of a 57% malathion concentrate diluted with 5 ml water over about 8.5 gm of bedding in each jar is recommended for permanent control of mange mites.

369. WELLS, H., ZACKIN, S. J., GOLDHABER, P. AND MUNSON, P. L. Increase in weight of the submandibular salivary glands of rats following periodic amputation of the erupted portion of the incisor teeth. *Am. J. Physiol.* 196: 827–30 (Apr.), 1959.

Periodic amputation of the erupted portion of the lower incisors of albino rats resulted in a marked increase in the wet and dry weight of the submandibular salivary glands as early as 7 days after the 1st amputation. Enlargement of both serous and mucous acini was observed, but no effect on the cells of the tubules could be detected. Amputation of the upper incisors alone did not result in enlargement of the submandibular glands. Hypophysectomy decreased the extent of the response to amputation of the lower incisors but did not abolish it. Chronic treatment with cortisone had no significant effect on the weight of the glands. A reflex neurologic explanation was offered as a tentative basis for understanding the phenomenon and as a starting point for further investigation. (Author's summary)

370. WILGRAM, G. F. AND INGLE, D. J. Renal-cardiovascular pathologic changes in aging female breeder rats. *A.M.A. Arch. Pathol.* 68: 690–703 (Dec.), 1959.

Pathologic changes of female rats, 12–15 mo. old, which were discarded as breeders by the Sprague-Dawley Company, are tabulated. Most of the rats had some degree of renal-cardiovascular damage, some had hypertension or stomach ulcers, benign tumors were common after the 1st yr. of life, malignant tumors occurred in a few. Male rats of the same strain and age had relatively little disease, suggesting the significance of the very active reproductive life of the females. An average mean resting blood pressure of 122 mm was found in young adult male rats, a blood pressure above 140 mm was rare. In a total of 220 old female rats, 42 had readings of 140 mm or above, the highest being 174 mm.

371. WINN, J. F. *Leptospira ballum* in small rodents. Letters to the Editor. *Lancet* 1: 1050 (May 16), 1959.

When white laboratory mice (*Mus musculus domesticus* (CFW)) were inoculated with serial dilutions of *Leptospira ballum*, subsequently made kidney tissue cultures were frequently positive but no demonstrable *Leptospira ballum* antibodies were found in the sera.

372. WRIGHT, J. F. Treatment of captive wild animals using an automatic projectile type syringe. *Vet. Med.* 54: 32–3 (Jan.), 1959.

The automatic projectile-type syringe provides a safe, economical method for the intramuscular administration of antibiotics, ataraxics, vaccines, hormones, etc., in captive wild animals.

373. YERGANIAN, G. AND MEIER, H. Spontaneous hereditary diabetes mellitus in the Chinese hamster (*Cricetulus griseus*). A preliminary report on clinico-pathological findings, genetic aspects, breeding and responses to hypoglycemic drugs. *Federation Proc.* 18: Abstr. No. 2026 (Mar.), 1959.

The main cause of diabetes is severe damage, vacuolar ("hydropic") degeneration and deficiency of beta cells. Concurrent alterations consist of intercapillary glomerulofibrosis and glycogen hepatosis. The trait is transmitted as a recessive factor with varying degrees of penetration in certain families of 4 major inbred lines. Each line varies in the incidence and date of onset of hyperglycemia. Littermates generally display similar levels of glucose and respond equally to therapy with insulin NPH, orinase, and DBI.

374. ZIMMERMANN, W. J., HUBBARD, E. D. AND MATHEWS, J. Studies on fecal transmission of *Trichinella spiralis*. *J. Parasitol.* 45: 441–5 (Aug.), 1959.

Investigations on the fecal transmission of *Trichinella spiralis* have been carried out using fox cubs and albino rats as donors, while swine, albino rats and fox cubs served as recipient hosts. The feces of experimentally infected animals have been examined by the Baermann technique to ascertain the number of larvae eliminated. The following factors were found to affect transmission: 1) time interval between infection and passage of feces by donor, 2) relative immunity of donor, and 3) number of trichinae ingested by the donor. About 95% of the larvae passing through the intestinal tract of the donors were recovered from feces eliminated

within 24 hr. after ingestion. Immune animals eliminated a larger percentage of the administered trichinae than did nonimmune animals. (Author's summary)

375. ZWEIFACH, B. W. Hemorrhagic shock in germfree rats. *Ann. N. Y. Acad. Sci.* 78, Art. 1: 315–9 (May), 1959.

Graded hemorrhage was used as the experimental condition to study the syndrome of irreversible shock. The experiments included germfree, monocontaminated and conventional rats of the Holtzman and Lobund strains. Irreversible shock could be produced in the absence of bacterial factors, in fact, no significant differences were noted in the responses of germfree and conventional rats. The value of germfree animals to studies of stress and shock is pointed out.

THE FOLLOWING ABSTRACTS, although located elsewhere in this bibliography, are related to the subject of this section.

Section 1: 2, 17, 22, 23, 31, 39, 44, 45, 47, 54, 59, 90, 101, 135, 151, 156, 162, 169, 174, 182, 184, 189, 191, 207, 228, 253, 254, 260, 263, 264, 277, 290, 294, 303, 309, 311, 323, 330, 335, 338, 341, 351, 353, 356, 357, 358, 359, 361, 366, 367, 375, 376, 377, 380, 391, 397, 404, 430, 449, 456, 462, 463, 481, 492, 507, 509, 512.

Section 3: 9, 11, 16, 17, 35, 36, 41, 53, 57, 61, 64, 67, 69, 74, 79, 80, 83.

Section 4: 14, 17, 18, 19, 23, 26, 29, 42, 45, 49, 58, 59, 66, 68, 69, 71, 72, 76, 77, 90, 93, 95, 96, 98, 101, 109, 112, 116, 117.

Section 5: 1, 19, 27, 34, 56, 61, 64, 75, 76, 80, 81, 82, 84, 89, 90, 99, 101, 102, 105, 108, 115, 118, 121, 123, 125.

Section 6: 11, 16, 17, 24, 30, 37, 40, 48, 49, 53.

Section 7: 44, 56, 85, 88, 108, 122, 123, 129, 141, 164, 172, 180.

Section 9: 18.

3. Nutrition: Food and Water Requirements; Diets; Dietary Supplements or Additives[1]

1. Pfizer, C. & Co. Livestock and poultry. Water and feed consumption table. (Advertisement)

A water and feed consumption table for livestock and poultry is given. The approximate daily feed consumption (lb) and daily water intake (gal) are, respectively:

Swine under 20 lb.: 0.5, 0.125; *20 lb.:* 1.5, 0.25–0.5; *60 lb.:* 3, 0.5–0.75; *100 lb.:* 5.5, 0.75–1; *200 lb.:* 7.5, 1.25–1.75. *Cattle 350 lb.:* 1–10, 1–5; *500 lb.:* 5–14, 2–6; *750 lb.:* up to 19, 10–15; *1000 lb.:* up to 21, 20 or more. *Sheep below 20 lb.:* 0.25–0.5, 0.5; *20 lb.:* 1–2, 0.5–1; *40–60 lb.:* 1–3, 1–3; *60–100 lb.:* 1–5, 1–3; *100–200 lb.:* 1–6, 1–4. *Chickens (per 100 birds) 2 wk. old:* 5, 1–1.25; *1 mo.:* 9, 1.5–2; *2 mo.:* 15, 3–3.5; *3 mo.:* 20, 4–4.75. *Turkeys (per 100 birds) 1 wk. old: 1.5, 1; 1 mo.:* 10, 3.5; *2 mo.:* 24, 7.5; *4 mo.:* 48, 17; 6 mo.: 67, 17.

2. Baumberger, J. P. and Allen, S. A new rat feeding device. *J. Lab. Clin. Med.* 20: 970–1 (May), 1935.

An apparatus which enables the rat to obtain compressed food pellets at will, without danger of contamination or loss of food, is described.

3. Tang, Y.-Z. A simple feeder for rats and mice. *Science* 87: 398 (Apr. 29), 1938.

A feeder to be used for controlled feeding of dry foodstuffs to rats and mice is described. The feeder consists of a tall cylindrical tin can with a removable lid and an entrance hole large enough for head, shoulders and front paws of the animal.

4. Morris, H. P. and Thompson, J. W. Convenient inexpensive device for quantitative hand feeding of mice. *J. Natl. Cancer Inst.* 1: 395–6 (Dec.), 1940.

A 1-cc tuberculin syringe fitted with a modified 18-gauge curved hypodermic needle with slightly enlarged tip is used. The mouse is held firmly with head up, the needle is passed over the tongue and through the pharynx into the esophagus while the animal's head is pushed upward and backward. The required dosage is then given. Mice have been fed daily vitamin supplements for 6 mo. without ill effects. For very small mice (5–8 gm wt.) a 20-gauge needle is used preferably.

5. Hogan, A. G. and Hamilton, J. W. Adequacy of simplified diets for guinea pigs and rabbits. *J. Nutrition* 23: 533–43 (June), 1942.

Three experimental diets were tested. The 1st contained dried yeast or yeast extract; the 2nd, which was not entirely adequate, contained pure vitamins only and no crude vitamin carriers; the 3rd contained the pure vitamins fortified with various liver fractions. The 1st and 3rd diet proved equally adequate for growth. Both rabbits and guinea pigs have reared litters successfully when the diet contained vitamins E and K; both species made normal growth without added K. For lactating animals the yeast level was kept at 15%. When all water-soluble vitamins were supplied as pure compounds now available, mortality was high and rate of growth subnormal.

[1] Arrangement is chronological by year of publication. A list of additional references, located in other sections of this bibliography, will be found on page 87.

6. Levin, L. A simple method for rapid tube feeding of rats. *Science* 96: 477–8 (Nov. 20), 1942.

The feeding is done as follows: a syringe is filled with the desired quantity of the liquid food mixture and then clamped securely to a ring stand by means of a burette clamp. The rat's mouth is held open by a string mechanism and the tube is inserted into the esophagus. One operator can feed 30–40 rats per hour. Normal and hypophysectomized rats of all ages, beginning at 35 days, have been given their entire food supply in this manner for long periods with excellent results.

7. Poth, E. J. A simple mechanical feeding device. *J. Lab. Clin. Med.* 27: 931–2 (Apr.), 1942.

An automatic feeder designed to feed every 4 hr. is described. Meat balls containing a daily dosage of drugs are skewered with pins and released to fall into the cage as the pins are withdrawn; a total daily food ration can be incorporated in the meat balls. The animals are kept slightly hungry so that they eat at the time food is delivered.

8. Sober, H. A., Mannering, G. J., Cannon, M. D., Elvehjem, C. A. and Hart, E. B. Nutrition of the guinea pig. *J. Nutrition* 24: 503–14 (Dec.), 1942.

Experiments showed that for adequate growth, guinea pigs require 3 factors in addition to those factors which have been demonstrated to be required by the rat and the chick: *1)* a factor supplied by 16% grass which is not supplied adequately by 16% yeast and 20 ml of winter milk; *2)* a factor supplied by 16% yeast which is not supplied adequately by 16% grass and 20 ml winter milk; *3)* a factor supplied by 20 ml winter milk which is not supplied adequately by 16% grass and 16% yeast.

9. Cooperman, J. M., Waisimen, H. A. and Elvehjem, C. A. Nutrition of the hamster. *Proc. Soc. Exptl. Biol. Med.* 52: 250–4 (Mar.), 1943.

The hamster grows poorly and fails to survive on synthetic diets which have proved to be adequate for rats. Better growth was found when synthetic diet is supplemented with whole liver substance or preparations from grass. The limiting factor in purified diets for the hamster is biotin and when biotin plus adequate amounts of both inositol and para-aminobenzoic acid are given, growth results are excellent. Neither nicotinic acid nor vitamin C, then, needs to be added to the diet. (Condensed from author's summary)

10. Mills, C. A. Heightened thiamine and choline requirements in tropical heat. *Proc. Soc. Exptl. Biol. Med.* 54: 265–6 (Dec.), 1943.

Weanling white male Sprague-Dawley rats showed optimal growth at 68°F on a diet containing 1 mg thiamine and 0.75 gm choline/kg food while for the same growth rate at 90°–91°F 2 mg thiamine and 5 gm choline/kg food were needed. The food eaten and the weight gained during the 3rd–5th wk. on the cold-room diet in rats kept at 68°F was 284 and 72.5 ± 4.16 gm, respectively, and 169 and 42.5 ± 2.12 gm in rats kept at 90°–91°F.

11. Hamilton, J. W. and Hogan, A. G. Nutritional requirements of the Syrian hamster. *J. Nutrition* 27: 213–24 (Mar.), 1944.

Hamsters grow at a normal rate and attain normal mature weights on simplified rations. The list of vitamins in the simplest satisfactory diet includes A, D, E, K, thiamine, riboflavin, pyridoxine, and pantothenic acid. If vitamin E is omitted from the diet the animals collapse and die in 4–18 wk. They may be rescued shortly after collapse by administration of vitamin E. If vitamin K is omitted from the diet the rate of growth is irregular but the animals reach maturity in nearly normal time. During the period of arrested growth the animals develop small hemorrhagic areas. If vitamins E and K are both omitted from the diet the animals apparently die from the vitamin E deficiency but they are also severely hemorrhagic. A high percentage of females bore at least 1 litter on simplified diets that contained nicotinic acid, choline, and inositol, in addition to the vitamins required during growth. The data are insufficient to decide whether biotin or *p*-aminobenzoic acid are essential for the hamster. Few females bore a 2nd litter and it was concluded that the hamster requires at least 1 unrecognized vitamin for reproduction. (Author's summary)

12. Campbell, H. L. Seasonal changes in food consumption and rate of growth of the albino rat. *Am. J. Physiol.* 143: 428–33 (Mar.), 1945.

A careful survey of food intake of a large number of rats maintained upon the same diet over a period of years shows the amount of food consumed to vary with the season of the years, the largest intake being in the winter months, the smallest in the summer months. The difference is unmistakably an actual difference, it being many times its probable error. This is established for the adult rat, 6 mo. of age and over, by data including over 900 cases for each 3-mo. season, and for the rapidly growing rat, 28th to 56th day of age, by 82 to 173 cases. (Condensed from author's summary)

13. Loosli, J. K. Feeding laboratory animals. *Ann. N. Y. Acad. Sci.* 46, Art. 1: 45–75 (June 15), 1945.

Nutritive requirements and diets of rats, rabbits, guinea pigs, mice, hamsters and cotton rats are reviewed on the basis of 210 references.

14. Parkes, A. S. Feeding and breeding of laboratory animals. I. Rat and mouse cubes, and cube containers. *J. Hyg.* 44: 491–500 (Sept.), 1946.

A diet consisting of 30% rolled or ground oats, 35% whole-meal flour, 5% dried yeast, 15% dried skimmed milk, 10% meat and bone meal, 3% cod-liver oil and 2% mineral mixture, fed to young mice and rats, gave growth curves as good or better than the much more expensive full cream diet (50% whole-meal flour, 27% dried full-cream milk, 12% dried yeast, 6% meat and bone meal, 3% cod-liver oil, 2% mineral mixture). The diets were fed in open pots placed in the cage. Experiments were also made with wire-mesh containers in which cubes could be fed. Consumption and requirements of these cubes by growing rats and mice were recorded.

15. Kellogg, C. E., Templeton, G. S. and Suitor, A. Feed required to produce 6-pound rabbits after weaning and conditions affecting their carcass grades and cuts. *U. S. Dept. Agr. Circ.* No. 819, Apr., 1949, 20 pp.

Feed requirements of New Zealand rabbits on different rations were studied. The effects of season, castration, age and disease on feed requirements were compared.

16. McCay, C. M. *Nutrition of the Dog.* 2nd ed. Ithaca, N. Y., Comstock Pub. Associates, 1949, 337 pp.

The ingredients of dog feeds are discussed. Special chapters are devoted to carbohydrates, fat, proteins, amino acid and protein derivatives, mineral requirements, fat- and water-soluble vitamins and testing of dog feed. Practical feeding and management, kennels and equipment, parasites and their control are also discussed. Books of interest to dog owners are reviewed.

17. Slanetz, C. A. Problems in the care and nutrition of dogs and other laboratory animals. *Proc. Animal Care Panel*, 1st Ann. Meeting, Nov. 28, 1950, pp. 43–5.

When space is limited dogs may be housed in cages with screen bottoms. When an animal refuses to eat, a dose of aureomycin generally restores the appetite in 6–8 hr. Parasites are controlled by a mixture of aureomycin and penicillin. Cats coming from farms are usually tempted to eat by offering them a variety of food. Coccidiosis in rabbits can be cured or prevented by feeding greens and antibiotics. Snuffles in rabbits are successfully treated with daily i.v. doses of 5–10 mg aureomycin. Monkeys suffering from loose stools respond to a high protein diet, a large supply of green foods and Vitamin C containing products and injections of liver extract. In the discussion Dr. Brewer points out that diarrhea in dogs receiving fresh horse meat for the 1st time is counteracted by a 3% addition of bone meal. The daily ration, for a 10 kg dog, of ½ lb. horsemeat, ½ lb. whole-wheat bread and other ingredients, is adequate. Some commercial dog foods need some extra fat.

18. Morrison, F. B. *Feeds and Feeding. A Handbook for the Student and Stockman.* 22nd ed., Ithaca, N. Y., Morrison Pub., 1951, 1207 pp.

Part I presents the fundamentals of animal nutrition: Various food nutrients; digestion, absorption, and use of food; measuring the usefulness of feeds; factors affecting value of feeds; proteins, fats, carbohydrates; minerals in livestock feeding; vitamins in livestock feeding; maintaining farm animals; growth, fattening, reproduction; production of milk, work, and wool; balanced rations, feeding standards; economy in feeding livestock.

Part II deals with feeding stuffs: Pasture and other forage; hay and haymaking; silage and crops for silage; legumes for forage; Indian corn and sorghums for forage; hay and pasture grasses, cereals for forage, straw; roots, tubers, and miscellaneous forages, poisonous plants and poisonous feeds; corn and oat grains and their by-products; other cereals and by-products; other seeds and their by-products; miscellaneous concentrates; manurial value of feeding stuffs.

Part III presents the feeding of farm animals: General problems in dairy husbandry; feeding and caring for dairy cows; raising dairy cattle; general problems in beef production; feed and care of beef cattle, methods and costs of beef production, veal production; general problems in sheep production; feeding and caring for sheep and lambs, fattening lambs, goats; horses and mules, general problems; feeding and caring for horses; general problems in swine husbandry; feeding and care of swine; general problems in poultry production; feeding and caring for poultry. In the appendix data are published concerning the composition of all important American feeding stuffs.

19. Richter, C. P. An ideal preparation for dissection of spinal, peripheral, and autonomic nerves of the rat. *Science* 112: 20–1 (July 7), 1951.

Rats fed single-food-choice diets consisting of water and a foodstuff such as dextrose, sucrose, olive oil, butter, casein or lactalbumin, continue to live for a long period of time, lose weight at a slow rate and after 40–60 days show no symptoms of nutritional deficiency except emaciation. These changes make them ideal specimens for dissection of spinal, peripheral and autonomic nerves and for differentiation between glandular and fatty tissue.

20. SLANETZ, C. A. Nutrition of small laboratory animals. *Proc. Animal Care Panel*, 2nd Ann. Meeting, Nov. 29–30, 1951, pp. 64–71.

Several commercial diets used for rabbits, guinea pigs, rats and mice are compared and body weight gains are tabulated. The composition of the diets is not given.

21. GIAJA, A. Sur la consommation alimentaire dans la lutte contre la chaleur. (Food consumption and environmental heat.) *Compt. rend.* 235: 818–20 (Oct. 13), 1952.

In the summer months when a dog was panting during the greater part of the day, it failed to consume all of a ration offered daily but still continued to gain weight. However, the same quantity of food was insufficient as soon as the heat declined and increased breathing ceased.

22. TALALAY, P. AND TAKANO, G. M. V. Apparatus for tube-feeding rats. *J. Lab. Clin. Med.* 40: 486–8 (Sept.) 1952.

The construction of a machine for tube-feeding rats with a highly viscous diet has been described. This apparatus permits quantitative dispensing of diet with ease and rapidity to large numbers of animals. (Author's summary)

23. ANONYMOUS. Feeding for energy requirements. *Gaines Dog Research Progr.* Spring, 1953, pp. 1, 4–5.

The fundamental requirements for dogs, under ordinary conditions, are estimated as 80 cal/kg body wt/day. The temperament of the individual dog, the activity, age and general environment may influence this figure. A new rapid method of calculating these factors is described. The method starts with measurements on the metabolic rate of the dog under standard conditions and adds to these increments for activity, age and fever. The following formulas were set up for calculating caloric requirements per day (x = wt. of dog in lb.): adult dog, 5–65 lb. body wt., $x(33 - 0.25x)$; adult dog over 65 lb. body wt., $18x$. Percentage increments to be added to basic food allowances for younger dogs: 1 yr. of age, 10%; 6 mo. of age, 30%; 3 mo. of age, 60%; for moderate and heavy work, respectively, 25% and 60%; for fever 7% for each degree Fahrenheit above normal; for pregnancy, parturition, lactation 20%, 25% and 50%–100%, respectively.

24. ANONYMOUS. Guinea pigs thrive on home grown bean sprouts. *Occupational Health* 13: 54–5 (Apr.), 1953.

Mung bean sprouts (grown in the laboratory) fed to guinea pigs through 3 generations were a satisfactory food supplement when compared with diets of kale and market vegetables. Other advantages were substantial saving in cost, ready availability of the feed. Time requirements for the animal caretaker were almost negligible.

25. BROWN, D., FERGUSON, I. D. AND RAMSAY, A. G. Guinea-pigs reared on a diet containing synthetic ascorbic acid. *J. Physiol.* (*London*), 121: 36–7P (June), 1953.

Guinea pigs receiving synthetic ascorbic acid added to a diet of green cabbage showed retarded growth compared with animals fed the greens without vitamin substitute.

26. CAMMIADE, M. E. AND LANE-PETTER, W. The feeding of sprouted grain to guinea pigs. *J. Animal Technicians Assoc.* 3: 72–5 (Mar.), 1953.

A method of producing green food in a forage chest in the laboratory is described. The succulent produce is fresh, clean, does not vary from season to season and has high ascorbic acid content. Though the capital outlay is high, maintenance costs are low. Adult animals so far will eat only stem and leaf of sprouted barley while the young ones eat the whole plant, shoot, root and seed.

27. DOWLING, M. T. AND FENTON, P. F. Nutrition of the mouse. XII. Comparison of several salt mixtures. *Proc. Soc. Exptl. Biol. Med.* 82: 16–7 (Jan.), 1953.

The relative merits of 5 commercially available salt mixtures in their ability to support growth, fat and mineral deposition in weanling mice of the C57 and I strains were studied. The salt mixtures used were (1) Hubbell, Mendel and Wakeman, (2) Fenton and Carr, (3) Wesson, (4) U.S.P. XII #2 and (5) McCollum-Simmonds #185.

28. FERGUSON, W. S. Hays and straws for laboratory animals. *J. Animal Technicians Assoc.* 4: 56–8 (Dec.), 1953.

A survey of hays and straws used in small animal husbandry and their relative feeding value.

29. NORTHCOTE, D. H. AND LEADER, V. R. A simple apparatus for the forced feeding of small animals. *J. Animal Technicians Assoc.* 4: 40–1 (Sept.), 1953.

A small inexpensive gag constructed of brass for forced feeding to rats, rabbits and guinea pigs is described. The gag enables animals to be fed at the rate of about 1 animal every 4 min.

30. UDALL, R. Nutrition of laboratory dogs. *Proc. Animal Care Panel*, 4th Ann. Meeting, Chicago, Dec. 2–3, 1953, pp. 5–16.

The requirements of a well-balanced feed are outlined; minimum levels of proteins, vitamins, minerals and fat are discussed. Since the energy requirement determines the level at which a ration needs to be fed, methods for estimating the energy requirement are described. Growth, activity, size, temperament and environmental temperature must also be considered.

31. WARNER, R. G., DAVIS, R. F., SPERLING, G. AND LOOSLI, J. K. Nutrition of small laboratory animals. *Proc. Animal Care Panel*, 4th Ann. Meeting, Chicago, Dec. 2–3, 1953, pp. 17–73.

The role of fats, proteins, vitamins and minerals in the diet of laboratory animals is discussed; the ingredients of some purified and some stock diets for rats and guinea pigs are listed. (Numerous references)

32. WINCHESTER, C. F. AND HENDRICKS, W. A. Energy requirements of beef calves for maintenance and growth. *U. S. Dept. Agr. Tech. Bull.* No. 1071 (July), 1953, 18 pp.

Data are given on growth rates and levels of energy intake of 16 pairs of identical twin calves. From these data equations were derived for the determination of energy requirements for growth and maintenance.

33. WORDEN, A. N. The feeding and husbandry of laboratory animals. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 1: 25–36, 1953.

The relationship between dietary and other environmental factors, such as chemical or microbial contamination, light, temperature, humidity and ventilation as well as between diet and physiological stress is reviewed. Several compound diets are discussed. The conclusion is drawn that nutritional requirements or

susceptibility to deficiency are influenced by a given set of environmental circumstances.

34. ANONYMOUS. Quarterly report to the editor on topics of current interest. Approximate relation of parts per million in diet to mg/kg/day. Some relations of drug toxicity in experimental animals compared to man. *Assoc. Food and Drug Officials U. S. Quart. Bull.* 18: 66 (Apr.), 1954.

The amounts of food (dry laboratory chow diet) consumed per day (liquids omitted) by a mouse of 0.02 kg body wt., young rat of 0.10 kg, older rat of 0.40 kg, guinea pig of 0.75 kg and rabbit of 2 kg are given as 3, 10, 20, 30 and 60 gm respectively. Data are given also for cat, dog, monkey, man, pig, sheep, horse and cattle.

35. NATIONAL RESEARCH COUNCIL, COMMITTEE ON THE HANDBOOK OF BIOLOGICAL DATA. *Standard Values in Nutrition and Metabolism,* edited by E. C. ALBRITTON. Philadelphia, Saunders, 1954, 380 pp.

The book contains tables arranged according to the following classifications: Nutrients; nutrients utilized by animal and plant forms; daily nutrient allowances; diets, culture media; nutrient and energy values of foodstuffs and feedstuffs; nutrient functions and signs of deficiency and excess; pathways and endways of metabolism; O_2 production; energy exchange. Animals include cat, dog, cattle, fox, mink, horse, swine, monkey, rat, chicken, hamster, mouse, cotton rat, sheep, turkey, fish, guinea pig, rabbit, and others.

36. ANONYMOUS. Nutritional disorders of baby pigs. *Nutrition News Bull.* 12: 4 pp. (Oct.), 1956.

Nutrient requirements of market stock pigs, pregnant and lactating females and breeding boars are listed. It is pointed out that the high mortalities in baby pigs are due largely to faulty nutrition of the sow during gestation and that pigs born from well fed sows have a higher survival rate.

37. ASSOCIATION OF AMERICAN FEED CONTROL OFFICALS. *Official Publication.* College Park, Maryland, 1956, 141 pp.

The definitions, standards and regulations pertaining to composition and labeling of various stock feeds are given. Official methods for the analysis of numerous constituents are included.

38. ELLINGER, F. Water intake of guinea pigs as parameter in oral drug therapy of experimental irradiation. *Proc. Soc. Exptl. Biol. Med.* 91: 172–4 (Jan.), 1956.

Drinking habits of normal and irradiated male guinea pigs on a diet of dry food and drinking water were studied. The conclusion was drawn that for an evaluation of drugs on the lethal effect of total body radiation oral administration of water-soluble drugs with drinking water appears possible with a sufficient degree of accuracy.

39. HEGSTED, D. M., GERSHOFF, S. N. AND LENTINI, E. The development of palatability tests for cats. *Am. J. Vet. Research* 17: 733–7 (Oct.), 1956.

A rapid and sensitive test using 15 adult cats for a 2-day period is described to screen the palatability of rations for cats; the data were evaluated by rank analysis. Some animals had definite food preferences; but when 2 foods were offered, the animals sometimes changed their preference. The fact that a ration was preferred did not necessarily mean that it was satisfactory from the nutritional standpoint.

40. MAYNARD, L. A. AND LOOSLI, J. K. *Animal Nutrition.* 4th ed. New York, McGraw, 1956, 484 pp.

The book contains the following chapters: General bases of nutrition; the nutrients and their metabolism; the measurements of body needs and feed values (determination of digestibility, nutritional balances, feeding standards, measures of food energy); nutritive requirements for body processes and production functions. Reference is made to domestic and laboratory animals. In the appendix nutrient requirements are listed for swine, poultry, cattle and sheep. A visual-aids bibliography, listing films on digestion and nutrition and animal feeding and suppliers of these films, is included.

41. ACKERMAN, C. J. Reversal of sulfaguanidine toxicity in the rat. *J. Nutrition* 63: 131–42 (Sept.), 1957.

Laboratory prepared diets (judged as complete by author), containing 1% sulfaguanidine, inhibited growth of weanling rats of the Holtzman strain. Meat meal in a concentration of 5% of the diet stimulated growth of rats which had ceased to grow due to ingestion of sulfaguanidine. When 5% meat meal was incorporated into the sulfaguanidine-containing diet, growth of the rats was as good or better than on diets containing neither sulfaguanidine nor meat meal.

42. BELLIS, D. B. Some problems in the nutrition of the baby pig. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 5: 89–93, 1957

The rapid growth of pigs presents problems in the artificial rearing of baby pigs. Pigs weaned at 5 wk. make satisfactory growth on rations consisting of 15% fish meal, 6% soybean meal, 19% flaked maize, 20% sucrose and 40% oat flour with vitamins A and D added. For pigs weaned from 3 days to 3 wk. a diet of 50% dried skim milk, 5% fat, 25% sucrose, 10% oatgroats, 10% fish meal plus vitamins, minerals and antibiotics is recommended. Tables listing the composition of sow's colostrum and of milk of the sow, mare, cow, goat and ewe are included.

43. BJÖRCK, G., OLSSON, B. AND DYRENDAHL, S. (Artificial feeding of puppies.) *Nord. Veterinärmed.* 9: 285–304, 1957.

Various formulas for feeding pups as reported in the literature are reviewed. Experiments with different formulas are described and the results are presented in tables and graphs showing the growth curves. The following formula is recommended: 800 ml of whole milk mixed with 200 ml of cream (12% butterfat), 1 egg yolk, 6 gm of bone meal, and 4 gm of citric acid dissolved in a small amount of water. The formula should have a total of about 2,000 units of vitamin A and 500 units of vitamin D which may be obtained by using one of the commercially available vitamin preparations. Pups are fed 6 times a day for the first 3 wk. by means of an ordinary nursing bottle. For small pups, a small rubber bulb from a medicine dropper may be used. After 3 wk. they can be fed from a dish and the number of daily feedings can be reduced to 5. The formula need be used for only 4 wk., after which solid food can be given. The amount of formula to give depends on the age. Pups should not be force fed. They should take enough so that the stomach can be barely palpated back of the costal arch. Pups of breeds of average size, at 3 days of age, should be fed daily an amount equal to about 15% to 20% of their body weight. Pups 3 wk. old may take a daily amount equal to 35% of their weight. (*J. Am. Vet. Med. Assoc.* 131: 433 (Nov. 1), 1957)

44. BOURNE, G. H. Some aspects of the feeding of dogs and other carnivora. *Lab. Animals Bureau, M.R.C. Lab. Collected Papers* 5: 81–7, 1957.

Nutritional and caloric requirements of dogs are discussed and the role of carbohydrates, fats, protein and vitamins in the diet are

reviewed. Domesticated and laboratory dogs generally need supplements providing vitamin A, B complex and D and possibly Ca and Fe, such as cod-liver oil and liver or dried brewer's yeast.

45. CASSIDY, J. The commercial manufacture of compressed diets for laboratory animals. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 5: 15–19, 1957.

The composition of diets for rabbits, guinea pigs, rats, mice and monkeys, the analysis of mineral mixtures, specimen batch and theoretical analyses of diets are tabulated. Variations in quality of the components have to be considered in order to obtain a fairly regular composition. The material should be thoroughly mixed before pelleting.

46. CUTHBERTSON, W. F. J. The nutritional requirements of rats and mice. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 5: 27–37, 1957.

The nutritional requirements of an animal depend upon its species and strain as well as on its physiological state and on factors such as nature of the diet and external environment. The requirements of rats and mice for their known dietary essentials and suggested optima are presented in tables. An extensive bibliography is included.

47. DAVIS, J. Some observations on lactation and food intakes in a colony of Chinchilla-Giganta rabbits. *J. Animal Technicians Assoc.* 7: 62–3 (Mar.), 1957.

The normal milk yield of the does, the natural feeding time of the young, the time spent in feeding and the amount of milk sucked at each feed were studied. The milk intakes of the young from birth or from the age of 7 days on were recorded over a period of 5–6 wk., for litters of 2, 5 and 8 young. Towards the end of the 3rd wk. the young commence to eat pellets starting with 3 gm/head and increasing to 56 gm by the 6th week.

48. DUPUIS, Y. Lactose et utilisation du calcium I. Influence du lactose sur les échanges calciques et sur le developpement du squelette du rat en croissance soumis à diverses conditions alimentaires. (Lactose and utilization of calcium. I. Influence of lactose on calcium retention and skeletal development in the growing rat at various diets.) *Compt. rend. soc. biol.* 151: 1722–5 (Oct.), 1957.

The addition of lactose to the diet of growing rats promotes the retention of Ca and produces an increased bone formation.

49. ELLIOTT, R. F. AND WHITEHILL, A. R. Placental and mammary transfer of ingested chlortetracycline in the rat. *Proc. Soc. Exptl. Biol. Med.* 94: 119–22 (Jan.), 1957.

Results with animals indicate that the maximum growth response to antibiotics occurs when they are included in the diets from earliest possible age. Since oral administration to young animals is difficult with certain species, administration through either placental or mammary transfer was studied. Pregnant female rats of the Wistar strain were fed diets containing chlortetracycline. When the prenatal diet contained 2 gm/kg, the antibiotic was present in the fetal tissues. At levels of 0.5 and 2.0 gm/kg of diet, detectable amounts were found in the mammary glands of the females and in tissues of the suckled young. The 2 gm/kg level of antibiotic improved the conception rate but did not affect the size of the fetuses or the number of young per litter.

50. FOLK, G. E., JR. AND FARRAND, R. L. Factors influencing the nutritional status of the hamster. *Proc. Animal Care Panel* 7: 245–52 (Dec.), 1957.

Three strains of hamsters when isolated in commercial type jar cages and fed stored commercial food pellets could not be maintained at normal weight levels although the same diet resulted in normal growth of albino rats of the Holtzman strain. Normal weight levels were restored in the hamsters by supplementing with a vitamin complex once a week and weights were maintained by feeding fresh food. Size of cage was not an important factor in maintenance of weight. Seasonal weight variations were noted in both males and females in so far as the animals lost weight as the hours of daylight decreased.

51. GRIFFIN, C. A., MCCAY, C. M., SPERLING, G. AND LLOYD, R. G. Stock diets for mice, rats, rabbits, dogs and Chinchillas. *Proc. Animal Care Panel* 7: 212–9 (Sept.), 1957.

Since meat scrap may be contaminated with stilbestrol and salmonella organisms a number of diets have been tested leaving out the meat scrap. Two of these mixtures resemble dog feeds commonly sold as pellets and meal. These have proved very satisfactory for the growth and reproduction of mice and rats. Biscuit type feeds which produce normal growth in dogs fail for mice and rats. Grain mixtures such as those used in Great Britain produce slower growth but satisfactory reproduction when fed to mice. A high quality of dried bread supplemented with butter or margarine is satisfactory for reproduction in the case of rats. Such dried bread fed with hay is capable of the maintenance of Chinchillas. The ingredients of a complete pelleted feed for rabbits are listed. This is also satisfactory for chinchillas and gives good reproduction when supplemented with oatmeal, wheat germ and bone meal. Pelleted rabbit feeds are not satisfactory for lambs. (Author's summary)

52. HEINEMANN, W. W., ENSMINGER, M. E., HAM, W. E. AND OLDFIELD, J. E. Phosphate fertilization of alfalfa and some effects on animal physiology. *Washington State College Agr. Expt. Sta. Tech. Bull.* No. 24, June, 1957, 23 pp.

Rabbits fed low-phosphorus hay showed decreased growth and breeding efficiency. Total inorganic phosphorus in the serum of 10-wk.-old animals was not affected; calcium, phosphorus, fat and ash contents of the humerus were increased; sodium and potassium contents of the bone ash were not affected. (Condensed from author's summary)

53. HOVE, E. L. AND HERNDON, J. F. Vitamin B_6 deficiency in rabbits. *J. Nutrition* 61: 127–36 (Jan.), 1957.

The daily vitamin B_6 requirement of rabbits of the California-white strain, for optimal growth, was found to be 39 gm, or, since the animals ate about 40 gm/day, the requirement may be said to be about 1 μg/gm of food. Vitamin B_6 deficiency resulted in a lowered growth rate, scaly skin of the ears, some acrodynia of nose, eyes, and forepaws, mild anemia, convulsions and finally death.

54. LABORATORY ANIMALS BUREAU, M.R.C. LABORATORIES. *The Nutrition of Laboratory Animals.* (*Collected Papers*, vol. 5) London, 1957, 93 pp.

For abstracts see: Bellis, D. B.; Bourne, G. H.; Cassidy, J.; Cuthbertson, W. F. J.; Hume, E. M.; Lane-Petter, W.; Paterson, J. S.; Ranadive, K. J.; Scott, P. P.; Singh, J. and Ray, A. P.; Weeks G. G.

55. LANE-PETTER, W. Modern ways of feeding laboratory animals. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 5: 7–13, 1957.

The advantages of cubed and pelleted compound diets are pointed out; some British cubed diets are discussed in detail.

56. Lewis, H. E. The feeding of laboratory animals. *J. Animal Technicians Assoc.* 8: 36–41 (Sept.), 1957.

A brief general survey of the main aspects of the feeding of such laboratory animals as rats and mice, cats, guinea pigs, monkeys, pigs and dogs is given. The criteria for assessing diets are: adequacy for growth, reproductive performance, mortality and morbidity rates and general resistance to disease. Dietary requirements of various species (cal/day and in some cases quantity and percentages of carbohydrates, proteins, vitamins, etc.) are discussed.

57. Paterson, J. S. The role of an adequate diet in the production of healthy guinea-pigs. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 5: 55–9, 1957.

The composition of Parkes's modified diet 18 is given and breeding performance of Dunkin Hartley strain guinea pigs, fed diet 18 and mated post partum and post weaning, is tabulated. Nutritional diseases caused by a diet deprived of hay are described. Attention is called to another disease of dietary origin which is characterized by soft tissue calcification.

58. Raica, N., Heywang, B. W., Vavich, M. G. and Kemmerer, A. R. The effect of fluoridated water on chick growth. *Poultry Sci.* 36: 1027–30 (Sept.), 1957.

Average weights, water and diet (all mash) consumption, and bone ash of male chicks at 5 wk. in winter, males at 6 wk. in summer, and males and females at 8 wk. in winter are given for controls and chicks fed F in the drinking water from 10–100 ppm.

59. Ranadive, K. J. Contribution to discussion. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 5: 39–41, 1957.

Groups of Swiss mice were fed for 3 yr. one of 5 different diets, the nutritive values of which are tabulated. A diet (No. 2) consisting of 70% cracked wheat, 20% cracked Bengal gram, 5% fish meal, 4% yeast and 1% shark-liver oil was found most satisfactory and very closely comparable in its results to the standard milk-powder formula. The cost of this diet was ⅓ that of the standard milk-powder diet.

60. Scott, P. P. Problems encountered in studying the nutrition of the cat (*Felis catus*). *Lab. Animals Bureau, M.R.C. Lab.,Collected Papers* 5: 43–53, 1957.

Mean growth curves and daily weight gains of healthy male and female kittens from newborn to 24 wk. of age, fed on a stock diet, are presented. Besides live weight gains other means of measuring the rate of growth in the living animal were studied. Skeletal growth was assessed by measuring the tail length each week. Other criteria concern the assessment of growth of the genital organs, the measurement of hemoglobin at different ages and the onset of sexual maturity in the female cat. Resistance to disease is also associated with an adequate diet. Nutritional requirements of cats with regard to protein, fat, carbohydrate, vitamin, and minerals are reviewed. The addition of antibiotics to the food is discussed.

61. Singh, J. and Ray, A. P. Studies on some aspects of the nutritional state of *M. mulatta mulatta* in nature and in captivity. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 5: 69–79, 1957.

Care and diet of *Macaca mulatta mulatta* is discussed. These wild-caught monkeys often showed diseases of bacterial, protozoal and helminthic origin but responded to treatment and a nourishing diet. Low-protein diets were poorly tolerated and led to anemia, loss of body weight, deterioration of the fur, liver damage and susceptibility to diseases. The general health remained good under a standard or a high-protein diet; the more expensive high-protein diet had no advantage over the standard diet with regard to general health of the animals.

62. Slanetz, C. A., Fratta, I. and Crouse, C. W. Stock diets, special diet supplements and their effects on laboratory animals. *Proc. Animal Care Panel* 7: 203–11 (Sept.), 1957.

The influence of special stock diets (commercial pelleted ration) and dietary supplements (high-protein meat-cereal supplement) on stock colony mice, rats and guinea pigs is shown in a series of tables, charts and slides. The data recorded include morbidity, mortality, growth rate, lactation performance, litter size, cannibalism and gross pathology. The addition of the dietary supplements resulted in an increase of productivity and litter size, a decrease in morbidity and mortality and elimination of cannibalism. General condition, coat and appearance of the animals improved. Feeding of soya oil and yeast supplements to guinea pigs maintained on a commercial pelleted diet favorably affected litter size and reproduction. A comparison was made of growth rate and reproduction performance of Sherman C and CWL rats on several stock diets in ordinary and air-conditioned quarters; the results were inconclusive.

63. Weeks, G. G. The assessment of the diets of laboratory animals. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 5: 21–6, 1957.

Growth as measured by weight gain and reproductive performance is most commonly used as criteria for the assessment of diets. The experimental method used is described. Other methods for determination of growth and development are discussed.

64. Baur, L. S. and Filer, L. J., Jr. Evaluation of lysine supplementation of infant formulas fed to rats. *J. Nutrition* 66: 545–54 (Dec.), 1958.

Male Sprague-Dawley rats, 21 days of age, were randomized into groups of 10 and fed one of the following rations for 6 wk.: powdered or liquid infant food, with or without added lysine, or a diet depleted of lysine. Animals fed the infant formula without added lysine grew considerably below optimum levels and were stressed with diarrhea and possibly lactose intolerance. Small lysine supplements stimulated appetite and growth but did not improve food or N efficiency while larger supplements depressed food and N efficiency. Rats on the depleted diet lost weight but returned to normal growth patterns when the depleted diet was followed by a complete ration.

65. Borchers, R. Effect of dietary level of raw soybean oil meal on the growth of weanling rats. *J. Nutrition* 66: 229–33 (Oct.), 1958.

The hypothesis that raw soybeans contain a "toxic" factor was disproved. It appears that the requirement for certain amino acids is increased when raw soybean oil meal is fed.

66. Browning, C. B., Parrish, D. B. and Fountaine, F. C. Effect of feeding low levels of diethylstilbestrol on gestation and lactation of rats. *J. Nutrition* 66: 321–2 (Nov.), 1958.

Adult female albino rats and their litters were fed low levels of diethylstilbestrol (0.6, 1.1 or 2.2 μg/100 gm body wt/day) for 3 days prior to breeding and during gestation and lactation. No measurable effect on conception or gestation was noted. However, growth of the young from lactating rats receiving DES in their rations was retarded significantly, indicating decreased lactation of these mother rats. (From author's summary)

67. EVERITT, A. V. The change in food and water consumption and in faeces and urine production in ageing male rats. *Gerontologia* 2: 21–32, 1958.

Changes observed with age in noninbred Wistar male rats were related to the cessation of growth and senility. Food and water consumption and production of feces/unit metabolic body size decreased from youth to middle age and then increased in old age and senility. Urine production remained relatively constant until old age and then increased. In order to separate effects of dying from those due to aging, data obtained from rats with a residual life of less than 100 days should be discarded in aging studies.

68. EXLEY, S. H. Nutrition of the cat. *J. Am. Vet. Med. Assoc.* 132: 538–9 (June 15), 1958.

Dietary requirements of the cat are discussed.

69. GUERRANT, N. B. AND STEEL, J. M. Some effects of aureomycin and penicillin on thiamine and riboflavin metabolism in growing rats. *Proc. Soc. Exptl. Biol. Med.* 98: 542–5 (July), 1958.

Both penicillin and aureomycin supplementation increased food intakes of rats on diets deficient in either thiamine and riboflavin or both, but neither antibiotic influenced food consumption when a diet adequate in thiamine and riboflavin was administered. Antibiotic supplementation seemed to improve food utilization particularly when thiamine intake was suboptimum and thiamine and riboflavin absorption was improved in the presence of antibiotics.

70. HARPER, A. E. AND SPIVEY, H. E. Relationship between food intake and osmotic effect of dietary carbohydrate. *Am. J. Physiol.* 193: 483–7 (June), 1958.

Rate of gain, food intake, stomach volume, dry weight and moisture content of the stomach contents, and the rate of stomach emptying were determined in rats at intervals after feeding low protein diets containing various carbohydrates. There was an inverse relationship between the capacity of the dietary carbohydrate to exert osmotic pressure and the food intake and rate of gain of rats fed for a single interval each day, but the positions of glucose and sucrose in the series were reversed under conditions of ad libitum feeding. There was a direct relationship between the capacity of the dietary carbohydrate to exert osmotic pressure and the stomach volume and moisture content of the stomach contents. Rats could be trained to consume an adequate quantity of a diet in a limited time more readily if the osmotic capacity of the dietary carbohydrate was low. (Condensed from author's summary)

71. MAGEE, A. C. AND MATRONE, G. Estrogenic activity of soybean forage. *J. Animal Sci.* 17: 787–91 (Aug.), 1958.

Since reproductive failures have been observed in rabbits fed diets containing large amounts of soybean material, an investigation of green soybean forage was conducted to determine whether it had any estrogenic activity. Fractions obtained by fractionation were tested by the mouse uterine weight technique. From 100 gm of green soybean forage (fresh weight), the estrogenic effect on the uterus of the immature mouse was equivalent to the uterine stimulation produced by approximately 0.03 μg of diethylstilbestrol.

72. MAMEESH, M. S. AND JOHNSON, B. C. The effect of penicillin on the intestinal synthesis of thiamine in the rat. *J. Nutrition* 65: 161–7 (May), 1958.

By the use of C^{14}-labeled thiamine it was found that the amount of available thiamine supplied by the intestinal microflora in Sprague-Dawley rats given diets either adequate or limiting in the vitamin was increased in the presence of 50 mg of penicillin/kg of diet. The amounts of the available microbial thiamine under the different treatments were estimated. In rats which were fed a sucrose diet adequate in vitamins, no thiamine other than that supplied in the diet could be detected in the liver. (Author's summary)

73. REID, M. E. Guinea pig nutrition. *Proc. Animal Care Panel* 8: 23–33 (Mar.), 1958.

The characteristics of the nutritional requirements of the guinea pig are given. *Protein or its equivalent:* medium to high (amino acids—high arginine, low methionine); *fats:* low or none if unsaturated fatty acids are supplied in suitable form and amount; *carbohydrates:* no special kind or definite amount necessary; *bulking agent:* beneficial but not absolutely necessary; *minerals:* high K and Mg; *vitamins:* high thiamine, folic acid and ascorbic acid, low niacin.

74. REID, M. E. *The Guinea Pig in Research; Biology—Nutrition—Physiology.* Washington, D. C., Human Factors Research Bureau, 1958, 87 pp.

This booklet describes the known dietary needs of the guinea pig in quantitative terms together with a brief account of some aspects of its physiology and the diseases associated with nutritional deficiencies.

75. BILD, C. E. Raising healthy pups. *Proc. Animal Care Panel* 9: 79–82 (June), 1959.

The relationship of the hemoglobin level in mother dog and pup is discussed. Suggestions are presented for an adequate nutrition of the pup.

76. CIZEK, L. J. Long-term observations on relationship between food and water ingestion in the dog. *Am. J. Physiol.* 197: 342–6 (Aug.), 1959.

The food-water intake relationship was studied in 18 beagle or hound-like dogs over a period of 7 yr. Single day observations were unreliable because of daily variations but the mean of 10 successive observations gave consistent results over a period of 3–4 yr. At a constant composition of the diet a quantitative linear relationship between food and water intakes was noted. The daily drinking response of a dog on a uniform diet is tabulated for 6 wk. (20 references)

77. DETHIER, B. G. Feeding behavior in the insect. *Am. J. Med. Sci.* 237: 404 (Abstr.) (Mar.), 1959.

Feeding in insects is initiated and driven by peripheral sensory input and terminated by negative feedback from the stomatogastric nervous system. The stimulating effectiveness of a food rather than its nutritional value is the crucial factor regulating feeding behavior.

78. FORBES, M., PARK, J. T. AND LEV, M. Role of the intestinal flora in the growth response of chicks to dietary penicillin. *Ann. N. Y. Acad. Sci.* 78, Art. 1: 321–7, 1959.

Comparison of the growth of germfree and conventionally reared chicks demonstrates that on adequate diets one or more components of the intestinal flora inhibit growth. Certain organisms commonly found in the chick's gut (*E. coli, L. lactis,* and *S. liquefaciens*), when implanted in chicks free of all other bacteria, do not depress their growth. However, *Cl. welchii* type A, another component of the intestinal flora, was found to depress the growth rate of otherwise germfree chicks. Penicillin in the diet largely overcame the growth depression caused by *Cl. welchii.* Thus penicillin, which had no effect on the growth of germfree chicks or on that of

conventional chicks reared in "clean" quarters, stimulated the growth of chicks with a defined intestinal flora by inhibiting bacteria that retarded growth. (Author's summary)

79. GERSHOFF, S. N. The nutritional requirements of cats. *J. Am. Vet. Med. Assoc.* 134: 139–41 (Feb. 1), 1959.

Weanlings need about 250 cal/day/kg of body weight, while kittens several mo. old and inactive adults need only 150 and 60 cal., respectively. Although precise fat requirements are not known, high-fat diets are more palatable and appear necessary for best growth when purified rations are fed. Protein requirements of cats seem to be higher than of other animals, including dogs. Diets containing as much as 30% ash have been fed to cats for a year without causing urinary calculi. Clinical signs of avitaminosis are tabulated, as are the vitamin supplements given to cats at the author's and one other laboratory. (Author's summary)

80. GREAT BRITAIN MINISTRY OF HEALTH. *Salmonella* organisms in animal feeding stuffs and fertilizers. *Bull. Ministry of Health* 18: 26–35, 1959.

An examination of 1,262 samples of organic fertilizers and animal feeding stuffs revealed that *Salmonella* was present in many products; 88 *Salmonella* serotypes were isolated, including 6 new types. In general, less than 100 *Salmonella* organisms were found per 100 grams. Anthrax bacilli were found in 5 out of 103 samples of bone meal and hoof and horn products. (From author's summary)

81. HORN, K. H. "Nährkonzentrat", ein Standardfutter für kleine Laboratoriumstiere. ("Nutritive concentrate," a standard feed for small laboratory animals.) *Pharmazie* 14: 274–6 (May), 1959.

A food concentrate was prepared from whole-grain wheat, milk powder, potato flour, cod-liver oil and feed lime. It proved adequate for growth and maintenance of rats and mice and can be stored for about 1 yr. A mouse consumes 3.5–4.0 gm/day of this concentrate, a rat 7.0–8.0 gm/day.

82. KAPLAN, M., CAMPBELL, S. L., JOHNSON, L., PAPAMICHAEL, A., SPARER, R. AND WEINBAUM, M. Growth of body weight and manipulation of food motivation. *Science* 129: 1673–4 (June 19), 1959.

In experiments dealing with motivation for food, or where hungry animals are required, some type of operational specification of food deprivation must be selected. A common technique for manipulating this variable is rhythm feeding where animals are allowed to eat ad libitum for a fixed interval at certain hours. Individual growth curves were used in random-bred male Wistar albino rats to estimate ad libitum-feeding weights. This procedure was found to be feasible in heterozygous animals, but it was limited by the occurrence of changes in growth. Such a change in the rate of growth appeared at 24 wk. in Wistar rats and as early as 18 wk. in CD rats.

83. LUCKEY, T. D. Nutrition and biochemistry of germfree chicks. *Ann. N. Y. Acad. Sci.* 78, Art. 1: 127–65 (May), 1959.

Cages for rearing germfree chickens are described and illustrated. Vitamin and protein losses incurred during sterilization of the diets are compensated by supplements. Germfree chickens require for growth the vitamins A, D, E, K, thiamine, riboflavin, niacin, biotin and folic acid. The composition of a practical diet and nutrient losses in a syntype diet are tabulated. Tissues of chicks in different deficiency states are analyzed. Mono- and dibiotic chickens are compared.

84. MISLER, S. AND KLECAK, G. An automatic watering system for use in animal cages. *Proc. Animal Care Panel* 9: 67–70 (June), 1959.

The construction and successful operation of an automatic watering system that provides an adequate and continuous supply of fresh water without the need for frequent cleaning of equipment, is reported.

85. PLEASANTS, J R. Rearing germfree cesarean-born rats, mice, and rabbits through weaning. *Ann. N. Y. Acad. Sci.* 78, Art. 1: 116–26 (May), 1959.

Germfree rats, Swiss mice and rabbits were successfully hand-reared by adopting a forced-feeding technique. Mortality among hand-reared rats and rabbits was chiefly the result of feeding more diet than the animal could handle. C_3H mice, however, were lost mainly through a pulmonary syndrome. Growth and development were subnormal during the suckling period but the diet did not create permanent handicaps.

86. PRENTISS, P. G., WOLF, A. V. AND EDDY, H. A. Hydropenia in cat and dog. Ability of the cat to meet its water requirements solely from a diet of fish or meat. *Am. J. Physiol.* 196: 625–32 (Mar.), 1959.

The physiology of hydropenia was studied in cats and dogs placed on a diet of *1*) no water, no food, *2*) water ad libitum, no food or *3*) food, no water.

87. PYE, O. F., TAYLOR, C. M. AND FONTANARES, P. E. The effect of different levels of ascorbic acid in the diet of guinea pigs on health, reproduction, and survival. *Federation Proc.* 18: Abstr. No. 2132 (Mar.), 1959.

Breeding lots of guinea pigs were fed a commercial ration supplemented with 2, 4, 6 or 8 mg/day of ascorbic acid, respectively, through life. Animals receiving the highest level of ascorbic acid had the best average reproductive record; they had more pregnancies with a longer average reproductive period and a larger number of young. The females on 4 and 6 mg ascorbic acid had better reproductive records than those on 2 mg/day. Mortality dates are given for all groups.

88. SHORT, D. J. AND GAMMAGE, L. A new pelleted diet for rabbits and guinea pigs. *J. Animal Technicians Assoc.* 9: 62–9 (Mar.), 1959.

A new pelleted diet, S.G.1, composed of 10% best white fishmeal, 20% grassmeal, 40% bran, 12% Sussex ground oats and 18% middlings, was devised to take the place of Diet 18. The new diet had a comparatively high protein content and was less prone to deterioration than Diet 18. Feeding tests with rabbits and guinea pigs showed that the new diet is satisfactory for the breeding and growth of guinea pigs if supplemented by fresh greenstuff and for rabbits if supplemented by hay only. An assessment of cost of feeding rabbits and guinea pigs with the new diet is presented.

89. SLANETZ, C. A. Problems in dog diets. *Gaines Dog Research Progr.*, Winter 1958–59, pp. 3–4.

Problems in dog nutrition concern obesity control, feeding of older animals, supplementation of inadequate diets, palatability, etc. Studies were made concerning the best ratio of meat, protein and fat in the diet, and the beneficial effect of fresh diets is pointed out.

90 STELLAR, E. Feeding behavior in the rodent. *Am. J. Med Sci.* 237: 404–5 (Abstr.) (Mar.), 1959.

Feeding behavior in the rodent is determined jointly by sensory stimuli, internal environment, central neural mechanisms and learning or habit.

91. WOSTMANN, B. S. Nutrition of the germfree mammal. *Ann. N. Y. Acad. Sci.* 78: 175–82 (May), 1959.

Results of feeding a semisynthetic and practical diet to germfree rats, Swiss mice, rabbits and guinea pigs are described.

THE FOLLOWING ABSTRACTS, although located elsewhere in this bibliography, are related to the subject of this section.

Section 1: 28, 39, 45, 52, 87, 97, 101, 135, 151, 162, 169, 178, 183, 185, 188, 194, 195, 254, 256, 263, 265, 311, 318, 332, 365, 373, 381, 384, 385, 386, 387, 388, 403, 426, 455, 462, 463, 481, 482, 483, 492, 493, 494, 510, 516, 517.

Section 2: 3, 9, 18, 24, 30, 51, 57, 60, 70, 81, 90, 93, 98, 102, 103, 104, 115, 120, 122, 135, 144, 168, 174, 191, 201, 216, 219, 244, 252, 258, 271, 275, 279, 298, 319, 330, 345, 346, 355, 361, 364, 366.

Section 4: 5, 6, 7, 10, 11, 13, 14, 16, 22, 23, 26, 31, 33, 43, 45, 49, 66, 69, 76, 78, 81, 83, 87, 90, 91, 98, 100, 109, 111, 112, 117.

Section 5: 1, 8, 19, 27, 28, 34, 38, 40, 49, 53, 56, 57, 61, 67, 72, 75, 76, 81, 90, 93, 94, 99, 102, 104, 109, 110, 117, 118, 123, 133.

Section 7: 75, 153, 154, 156.

4. Breeding Programs: Design and Operation of Production Colony[1]

1. Poiley, S. M. A systematic method of breeder rotation for non-inbred laboratory animal colonies. *Proc. Animal Care Panel*, mimeo, (no date), 12 pp.

A practical, simplified method of selecting breeding animals for randomly mated animal colonies, without cumbersome bookkeeping, is reported. The unit plan applied has proved satisfactory for large-scale production of all common laboratory animals. The duration of the breeding cycle is determined by the reproductive biology of the species involved.

2. Greenman, M. J. and Duhring, F. L. *Breeding and Care of the Albino Rat for Research Purposes.* 2nd ed. Philadelphia, Wistar Institute of Anatomy and Biology, 1931, 121 pp.

Chapters are presented on the following topics: Use of the rat as a research animal; colony building and cages; food; breeding; diseases; transportation; marking of animals.

3. Bruce, H. M. and Hindle, E. The golden hamster, *Cricetus* (*Mesocricetus*) *auratus* Waterhouse, notes on its breeding and growth. *Proc. Zool. Soc.* (*London*) 2: 361, 1934.

General description of the growth and reproduction of a stock kept for 8 generations under laboratory conditions. The gestation period averages 16 days. There are 6–7 young per litter. Sexual maturity is attained at 7–8 wk. (*Biol. Abstr.* 9: 20609, 1935.)

4. *Culture Methods for Invertebrate Animals.* A Compendium Prepared by American Zoologists under the Direction of a Committee from Section F of the Am. Assoc. Adv. Sci.: P. S. Galtsoff, F. E. Lutz, P. S. Welch, J. G. Needham, Chairman, assisted by many specialists. Ithaca, N. Y., Comstock Pub. Associates, 1937, 590 pp.

The book has been prepared as an aid to studies that require living animals in continuous supply. Methods for rearing the following invertebrate animals are recorded: Protozoa, Porifera, Coelenterata, Plathelminthes, Nemathelminthes, Trochelminthes, Bryozoa, Annelida, Nemertinea, Arthropoda, Mollusca, Echinodermata, Chordata.

5. Laidlaw, P. Maintenance of the golden hamster. *Intern. J. Leprosy* 7: 513–6 (Oct.–Dec.), 1939.

Hamsters should be housed in galvanized wire cages (.25-in. mesh) which are placed in shallow metal trays. The dimensions suitable for breeding are 15.5 x 9 x 8.5 in. in a tray 16 x 9.5 x 1 in. Temperature should be kept at 65°–75°C. Hamsters breed at the age of 8–12 wk., producing yearly 2–3 litters of 4–5 young each. Gestation is 16 days. The young can be handled at 14 days and weaned at the 4th–5th wk. Hamsters can be maintained on a well balanced diet with a certain amount of greenstuff; meat or liver should not be included in the ration. Handling should be done by attendants to whom they are accustomed.

6. Mathis, M. Technique d'élevage des souris blanches. (Technique of raising white mice.) *Presse méd.* 49: 37–8 (Jan. 8–11), 1941.

The raising of white mice in the Pasteur Institute in Dakar is described. Good results were obtained by feeding a vitamin-supported diet and by providing sufficient drinking facilities in the cages. The importance of good ventilation and spaciousness of the cages is pointed out: groups of 10 mice live comfortably in 25 compartments measuring 20 x 20 cm each whereas 250 mice put together into an undivided cage of 1 m^2 cannot thrive. Mice housed in glass cages are inactive during daytime but become active at night. Therefore they are given food in the evening rather than in the morning. A temperature of 25°C is the most favorable for white mice raised in hot climates. For breeding purposes, one male, 4–6 mo. old, should be paired with 10 females, 2 mo. old. Gestation takes about 20 days; the young are separated from the mothers at 1½ mo. A female may have 5–6 litters.

7. Bond, C. R. The golden hamster (*Cricetus auratus*): care, breeding and growth. *Phys. Zool.* 18: 52–9 (Jan.), 1945.

A study of 1500 animals over a 2-yr. period led to the following conclusions: Hamsters should be housed in metal cages and provided with a varied diet of grain and fresh vegetables. Matings occur usually at night; principal factors affecting breeding are diet, temperature and age of females; length of gestation period is 15 days and 21 hr. Postnatal development is rapid; 8-day-old hamsters get along without maternal care. The mean age at first littering is 73.6 days; the mean litter size is 6.93 ± 0.23 animals with a standard deviation of 2.414. (Condensed from author's summary)

8. Hartman, C. G. The mating of mammals. In: Farris, E. J., Conf. Chairman. Animal Colony Maintenance. *Ann. N. Y. Acad. Sci.* 46, Art. 1: 23–44 (June 15), 1945.

General mating techniques are reviewed and controlled breeding is described for the rat, mouse, guinea pig, rabbit, golden hamster, opossum, dog, cat, fox, horse and monkey.

9. Hutt, F. B. Genetic purity in animal colonies. In: Farris, E. J., Conf. Chairman. Animal Colony Maintenance. *Ann. N. Y. Acad. Sci.* 46, Art. 1: 5–20 (June 15), 1945.

Littermates differing by a simple unifactorial mutation may be extremely different in form, in physiology and in viability. To reduce genetic variability, the laboratory worker is recommended to select from the existing breeds and strains those already proved suitable for his purpose, and to reduce heterozygosity still further by the most intense form of inbreeding that is compatible with vigor and good reproduction. Results to be expected with different degrees of inbreeding and with selection are discussed. (Condensed from author's summary)

10. Gale, L. C. *Raising Hamsters for Science.* Goodland, Kan., L. C. Gale, 1946, mimeo, 36 pp.

[1] Arrangement is chronological by year of publication. A list of additional references, located in other sections of this bibliography, will be found on page 98.

Housing, feeding, breeding, maintenance and care, standards, transportation, time requirements and use of golden hamsters are discussed.

11. BRUCE, H. M. AND EMMENS, C. W. The feeding and breeding of laboratory animals. VII. Methods of testing the adequacy of diets for breeding mice. *J. Hyg.* 46: 315–24 (Sept.), 1948.

This application of factorial design to the testing of diets for breeding mice is described. The use of a system of monogamous mating, by which the females have a continuous series of pregnancies with concurrent gestation and lactation, is advocated for such tests. Present indications are that a high-wheat content or a high-yeast content is desirable in the diet of breeding mice. A diet containing a considerable proportion of full-cream milk was very effective for breeding mice, but it is not yet certain that this constituent is necessary. (Author's summary)

12. BRUCE, H. M. AND PARKES, A. S. Feeding and breeding of laboratory animals. VIII. Breeding of guinea-pigs. *J. Hyg.* 46: 434–7 (Dec.), 1948.

The use of the monogamous system for guinea pigs and especially for a small pilot colony designed to supply fully recorded replacement stock to a mass breeding colony was investigated. Average litter size, birth weight and rate of growth and mortality of the young are reported.

13. BREWER, J. H. Routine "safety" tests on drug products and the organization and maintenance of a requisite mouse colony. *J. Am. Pharm. Assoc. Sci. Ed.* 38: 165–8 (Mar.), 1949.

The equipment, care and maintenance of the mouse colony are described and illustrated. Illustrations show breeder box, stock box and sterilizer pan; expanded view of the first two; breeder units; stock boxes; mice under test; and feeding and watering devices. The average mouse drinks about 4 ml water and eats 4 gm food (Purina Lab. chow) daily. Temperature control in the room to a fairly constant 70–80°F is important. If this is not maintained, serious damage or death may result to the breeding animals, and/or the average output of young is considerably lessened. Time requirements for care and maintenance are also given.

14. BARTOS, F. J. Puppy management. *Dog Research News* 1, No. 3, 1950, 4 pp.

Management of a production colony is described. The following topics are discussed: breeding, delivery, caging, feeding and diseases.

15. BARTOS, F. J. Mechanical techniques of breeding dogs. *Dog Research News* 1, No. 6, 1950, 4 pp.

Estrus, mating and artificial insemination are discussed.

16. HALL, R. A. The effect of controlled artificial illumination on rat breeding. *J. Animal Technicians Assoc.* 1: 7–17 (Sept.), 1950.

Rat breeding can be carried out successfully in an artificially illuminated room from which all natural daylight has been excluded. The experiments confirmed that more regular estrus cycles may be obtained by subjecting the female rats to controlled artificial light. A supplemented Thomson cubed diet together with controlled illumination induced a winter breeding performance comparable to that obtained in the summer months.

17. FAINSTAT, T. D. Hereditary differences in ability to conceive following coitus in mice. *Science* 114: 524 (Nov. 16), 1951.

Five genetically different stocks of mice (A, C57 black, black and tan, a stock carrying the mutant "Naked" and a genetically heterogeneous stock), when injected with cortisone, were found to fall into 2 distinct groups with respect to incidence of cleft palate in their offspring. Strain differences were also found in the incidence of pregnancy following coitus.

18. LUND, E. E. Mortality among hutch-raised domestic rabbits. *U. S. Dept. Agr. Circ.* No. 883, 1951, 14 pp.

A study was undertaken at the U. S. Rabbit Experiment Station in Fontana, Calif., to provide a tentative standard for rabbit raisers and investigators in comparing their death losses. The mortality at different ages from various causes for a 3 yr.-period is tabulated. Enteritis was responsible for more mortality among unweaned young than was any other disorder; pneumonia was the greatest single cause of death in mature animals; coccidiosis was not a factor in mortality. Mortality was higher in breeding does than in bucks, but does not producing litters showed about the same mortality as the bucks.

19. NELSON, J. B. Studies on endemic pneumonia of the albino rat. IV. Development of a rat colony free from respiratory infections. *J. Exptl. Med.* 94: 377–86 (Nov. 1), 1951.

A colony of albino rats was developed from 3 not germfree breeders originally delivered by cesarean section and artificially reared in the laboratory. The colony has been maintained under quarantine for about 3 yr., in the absence of any demonstrable involvement of the respiratory tract or the middle ears. At necropsy pleuropneumonia-like organisms, *Streptobacillus moniliformis*, and the virus-like agent associated with endemic pneumonia were not recoverable from the lungs or nasal passages.

20. RUGH, R. *The Frog, its Reproduction and Development.* Philadelphia, Blakiston, 1951, 336 pp.

21. SAWIN, P. B. Problems in breeding laboratory stocks of rabbits. *Proc. Animal Care Panel* 2nd Ann. Meeting, Nov. 29–30, 1951, pp. 72–82.

Preliminary evidence is presented which indicates that maximum reproductive capacity is modified by at least 5 major genetic factors. These factors are fertility, fecundity, lactation, growth and maternal behavior. The analysis of these variations have significant applications in the development of useful isogenic stocks for experimental biology.

22. ALEXANDER, D. P. AND FRAZER, J. F. D. Interchangeability of diet and light in rat breeding. *J. Physiol. (London)* 116: 50–1P (Jan.), 1952.

Wistar albino rats and Lister hooded strains fed a diet composed chiefly of whole meal, ground oats and fish meal, showed the same mating performance on 8- and on 13-hr. periods of light. However, extension of the lighting period from 8 to 13 hr. improved mating performance of rats on an apparently inadequate white-meal stock diet.

23. BENNETT, J. The management of chickens for experimental purposes. *J. Animal Technicians Assoc.* 3: 17–8 (June), 1952.

Breeding, housing, feeding and diseases of chickens are discussed.

24. BURNS, M. *The Genetics of the Dog.* Farnham Royal, Bucks, England, Commonwealth Agricultural Bureaux, 1952, 122 pp.

The book contains a digest of the world's technical studies of dog genetics. It has chapters on Mendelian theory, reproduction,

conformation, physiological peculiarities, abnormalities and disease, behavior and mental attributes, coat, skin and color, breeding systems and use of genetic formulas. (Condensed from a review in *Science* 117: 310, 1953)

25. FALCONER, D. S. The improvement of laboratory animals by selective breeding. *J. Animal Technicians Assoc.* 3: 9–16 (June), 1952.

General qualities required in laboratory animals are *1)* general health, vigor and disease-resistance, *2)* high productivity, *3)* good mothering ability and *4)* tameness and ease of handling. In selecting some breeding stock, hereditary constitution and environment provide the best "breeding values." When litters are weaned, selection of the mothers for productivity and mothering ability can be made, and when the animals are ready to be mated, selection for health and minor characteristics can be made. The rate of improvement under selective breeding is controlled by the intensity of selection and the generation interval. By inbreeding, hereditary variability is reduced and uniformity is obtained. Principles of inbreeding are discussed in detail.

26. POILEY, S. M. A breeding program for laboratory mice. *Proc. Animal Care Panel* 3rd Ann. Meeting, Dec. 3–4, 1952, pp. 92–106.

A program is described in which each breeding unit always contains 3 females, for as a pregnant female is removed she is replaced by another female to be mated. Breeders are selected at weaning, i.e. at age of 4 wk. and are discharged at the age of 11.5 mo. Females generally give birth to their 1st litter at the age of 69 days. By removing pregnant mice to individual cages for completion of gestation and nursing periods, an average total of 4–5 litters per female or 35 weaned offspring is produced per mother. General directions are given concerning disease and sanitation, housing, nutrition, behavior patterns and caretaker personnel.

27. PRICE, W. T. An experience in cat breeding. *J. Animal Technicians Assoc.* 3: 43 (Sept.), 1952.

A production colony of cats is described; their feeding and care of the young is discussed.

28. ROBSCHEIT-ROBBINS, F. S. A breeding program for laboratory dogs. *Proc. Animal Care Panel* 3rd Ann. Meeting, Dec. 3–4, 1952, pp. 70–7.

A dog suitable for studies of liver physiology with attendant surgery to permit studies of blood destruction was obtained by interbreeding a bull terrier with a Dalmatian. Housing, feeding, and a breeding program is discussed.

29. ZUCKER, T. F. Concerning rat breeding programs. *Proc. Animal Care Panel* 3rd Ann. Meeting, Dec. 3–4, 1952, pp. 78–91.

Suggestions are made for the production of better defined rats of more uniform quality. The problem of chronic lung infections in rat colonies, the growth pattern and the variability of body weight is discussed. The incidence of lung disease could be significantly lowered by using progeny testing in selective breeding. Growth and body weight are dependent on genetic and environmental factors.

30. BEACH, F. A. AND KAGAN, J. Effects of early experience on mating responses in male rats. Abstract of paper presented at the Annual Meeting of the National Academy of Sciences April 27–29, 1953. *Science* 117: 465 (May 1), 1953.

The number of males displaying copulatory behavior was the same in animals with or without early experience. But the complete mating pattern, including ejaculation, was more than twice as frequent for males lacking previous contact with other rats than for animals that had previously been exposed to either males or females during a conditioning period.

31. BRUCE, H. M. Feeding and breeding of laboratory animals. XIII. A note on the use of autoclaved stock diet for breeding mice. *J. Hyg.* 51: 258–9 (June), 1953.

The stock diet for rats and mice, diet 41 cubed, can be rendered sterile to broth by autoclaving at 15 lb/sq. in. for 20 min. without impairment of the nutritive value for breeding mice. (Author's summary)

32. CHARLES, R. T. An experiment to show the effect of strong light on lactating female rats. *J. Animal Technicians Assoc.* 4: 54–5 (Dec.), 1953.

Strong light had a harmful effect on the rearing of litters of Wistar albino rats. The animals became emotionally disturbed which resulted in increased defecation and urination, aggressive behavior and an endocrine inequilibrium involving the lactogenic hormones.

33. COX, H. W. AND PATERSON, J. S. The breeding of rabbits for biological use. *J. Animal Technicians Assoc.* 4: 31–4 (Sept.), 1953.

Breeding programs and nutrition adequate for reproduction are discussed.

34. EATON, O. N. The development of the genetic concept of controlled pure animal strains. *Proc. Animal Care Panel* 4th Ann. Meeting, Chicago, Dec. 2–3, 1953, pp. 130–9.

The following points are emphasized. Inbreeding is *1)* useful in making a stock more homozygous, *2)* the most powerful means of making distinct families, *3)* useful in purging the stock of recessive defects and equally useful in propagating desirable qualities; *4)* it facilitates standardization of stock, generation after generation, with an assurance that individuals from that stock will perform as in the past; *5)* it is the severest way to test the real genetic worth of a sire or dam; *6)* it makes possible more effective selection between families; *7)* selected families can be intercrossed to restore genetic variability. (From author's summary)

35. ENGLAND, D. C. The development of a new experimental animal for medical research: the miniature pig. *Proc. Animal Care Panel*, 4th Ann. Meeting, Chicago, Dec. 2–3, 1953, pp. 173–7.

An anatomically normal miniature-size pig, weighing 60–70 lb., is produced at the Hormel Institute branch of the University of Minnesota through the use of inbreeding and selection of stocks arising from a cross of 3 wild stocks. These pigs are used in the study of a number of medical research problems.

36. FRINGS, H. AND FRINGS, M. Development of strains of albino mice with predictable susceptibilities to audiogenic seizures. *Science* 117: 283–4 (Mar. 13), 1953.

A program of selection and progeny-testing of mice for specific susceptibilities to audiogenic seizures is described. The 4 strains thus produced were developed from an originally random albino stock by variously inbreeding and outbreeding. Mice of one of the strains have a very low incidence of, or are nonsusceptible to, seizures. They are valuable for comparison with the highly

susceptible mice and for use in studies in which seizures are undesirable. Within limits of resources, breeding pairs are supplied to interested individuals for testing.

37. JAY, G. E., JR. New applications of genetic control to medical problems. *Proc. Animal Care Panel*, 4th Ann. Meeting, Chicago, Dec. 2–3, 1953, pp. 163–8.

Genetic control has been attempted by control of environment and heredity and by the use of litter mates. In cases where genetically uniform experimental material is necessary, such as in cancer research, the technique of close inbreeding (brother x sister or parent x offspring matings) is employed. This technique has been applied mainly to mice, but also to rats and guinea pigs and to a lesser extent to rabbits, hamsters, dogs, and cats. Other examples demonstrate how genetic uniformity can be utilized in medical research.

38. MORGAN, P. V. AND COX, G. J. Devices for small animal rooms. *Proc. Animal Care Panel*, 4th Ann. Meeting, Chicago, Dec. 2–3, 1953, pp. 192–3.

The following devices are described and illustrated: *1*) a combination unit of handle, card holder and water bottle holder for the cage; *2*) a copulation detection table for rats; *3*) a modification of a direct-reading balance for obtaining the birth and successive weights of small mammals.

39. MUNDY, A. E. Incidental mortality in a breeding unit. *J. Animal Technicians Assoc.* 4: 35–8 (Sept.), 1953.

Details are given of the mortality rate among mice and guinea pigs in a "closed" breeding unit for a period of 2.5 years. The figures clearly show that a higher mortality rate occurred in both species at weekends when relief workers were on duty. (Author's summary modified)

40. PATERSON, J. S. The provision of animals for research. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 1: 55–66, 1953.

Sources of supply, the different categories of users, the advantages and disadvantages of closed colonies for breeding are discussed.

41. ROWLANDS, I. W. Why do puppies die? *Gaines Dog Research Progr.*, Fall 1953.

The death rate among pups of 45 bitches (Airedales, foxhounds and mongrels) mated to Labrador and Airedale studs and the average litter size is tabulated. The influence of environmental temperature and nutritional factors on death rate is discussed.

42. SCARNELL, J. The control of infection in small animal breeding units. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 1: 49–54, 1953.

The following line of defense is suggested: *1*) Measures to prevent entry of infection into the animal houses; *2*) maximum separation of animals; *3*) early diagnosis of infections and vaccination of breeding stock wherever possible. Examples of experience with guinea pigs, dogs, mice and ferrets are presented.

43. BRUCE, H. M. Feeding and breeding of laboratory animals. XIV. Size of breeding group and production in mice. *J. Hyg.* 52: 60–6 (Mar.), 1954.

The production of weaned young from pairs or groups of 3, 4 and 5 mice, each containing 1 male, is compared. For long-term large-scale production, small breeding groups of 1 male with 2 females are proposed. (Author's summary)

44. ENGLAND, D. C., WINTERS, L. M. AND CARPENTER, L. E. The development of a breed of miniature swine. A preliminary report. *Growth* 18: 207–14, 1954.

The development of a miniature pig suitable for laboratory research work is described. (*See:* Lundberg, W. O. *Proc. Conf. on Research, Council on Research Am. Meat Inst., Univ. Chicago* 9th Conf., Mar. 22–3, 1957, pp. 109–13)

45. NATIONAL RESEARCH COUNCIL, INSTITUTE OF ANIMAL RESOURCES, COMMITTEE ON HANDBOOK (H. G. HERRLEIN, Chairman). *Handbook of Laboratory Animals.* (*Natl. Research Council Publ.* No. 317) 1954, 77 pp.

The nutrition of laboratory animals and diseases of chicken, mice, rats, guinea pigs, rabbits, monkeys, dogs, cats and frogs are discussed. Genetic standards are given by describing the existing stocks or strains. Sources of supply of mice, rats, guinea pigs and hamsters are reported and tests for which these animals can be used are listed. A bibliography of uses of laboratory animals and their general care and management is included.

46. YEATES, N. T. M. Daylight changes. In: HAMMOND, J., ed. *Progress in the Physiology of Farm Animals.* London, Butterworth & Co., 1954, pp. 363–92.

The following topics are discussed: Light effects as they affect breeding season and natural selection, period of gestation (implantation of blastocysts), coat shedding and moulting, milk production and growth; experimental light treatment with respect to intensity and wavelength and type of application; mechanism of light action; practical considerations concerning lighting of poultry houses, transfer of stock to a new environment and winter milk from goats.

47. BACHARACH, A. L. Some aspects of animal production for routine biological assay. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 3: 6–27, 1955.

Breeding programs for inbred rats and albino and fawn mice are discussed. Viability and fertility of these highly inbred strains were studied. Fluctuations in the fertility of albino rats showed a seasonal rhythm while no such influence was noted in piebald rats. The figures for 2 rat colonies demonstrated that in these strains brother-sister mating for 30–60 generations produced no detectable fall in fertility or loss of viability. A breeding program for assay work is outlined.

48 EDWARDS, R. G. Selective fertilization following the use of sperm mixtures in the mouse. *Nature* 175: 215–6 (Jan. 29), 1955.

Artificial insemination was carried out in mice using sperm from a number of inbred lines each containing a suitable genetic marker. The lines used were REB, G and C3H. Experiments showed that in sperm mixtures the chance of fertilization by a particular type may not be the same for all components of the mixture. Several different interpretations of this phenomenon were considered: the C3H sperm may be more efficient than that of the other 2 lines involved, or the C3H sperm may exert a specifically depressant effect on REB sperm.

49. GRAY, E. LEB. AND DERUM, J. W. The medical laboratories rat pilot colony. *U.S. Army Chemical Center, Chem. Corps. Med. Labs. Res. Rept.* No. 365 (May), 1955, 23 pp.

To fill a need for healthy animals from a single, known source, the Animal Ecology Branch established a rat pilot colony in May 1952. By controlling the rats' environment, by applying certain

principles of genetics, and by insisting on stringent hygienic and contact practices, the Branch sought to establish a small nucleus of animals which would be essentially free from pulmonary and parasitic disorders. By March 1954, post-weaning deaths dropped from 15.8% to 0.0%, pneumonic infections from a high of 60% to about 12%, and parasitic infections were no longer detectable. The "spinner" rat became a rarity. A production colony eventually supplanted the pilot colony so rat production could be increased fivefold. Improved control and record keeping methods prevented the accumulation of surplus animals, and better management techniques indicated that rats raised in the Animal Ecology Branch, Medical Laboratories, cost only about ⅔ as much as those purchased from commercial dealers. A planned personnel training program, coincident with the establishment and maintenance of the pilot colony, significantly increased the efficiency of the animal technicians. A record system was devised.

50. GRUNSELL, C. S. The problems of a curator. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 3: 87–92, 1955.

The management of a small breeding colony is discussed.

51. LABORATORY ANIMALS BUREAU, M.R.C. LABORATORIES. The Breeding of Laboratory Animals. (*Collected Papers* vol. 3) London, 1955, 92 pp.

For abstracts see: Bacharach, A. L.; Grüneberg, H.; Grunsell, C. S.; Mandl, A. M.; Michie, D.; Nichols, J. E., Perry, J. S.; Rowlands, I. W.

52. MANDL, A. M. The value of littermate controls in endocrinological research. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 3: 49–57, 1955.

The reduction of variability between animals of the same colony is a means of decreasing the number required for a statistically satisfactory experiment. Variability can be drastically reduced by crossing 2 inbred lines and using the first crosses for experiments. On the other hand, raising of first crosses in addition to the normal inbred stock can be avoided if an experiment is designed to compare the effect of different treatments on littermates. When littermates were used as controls, some figures were recomputed to demonstrate the variance due to genetical and environmental factors. Variance between littermates in reproductive cycles and endocrinological reactions is discussed. Costs of raising a colony of littermate and nonlittermate rats are compared.

53. MICHIE, D. Towards uniformity in experimental animals. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 3: 37–48, 1955.

Genetic and environmental conditions which promote uniformity are discussed. The ills of inbreeding, the so-called "inbreeding decline," and the beneficial effects of outcrossing are pointed out. For some purposes, as in the fields of serology and tissue grafting, genetic homogeneity, as obtained by inbreeding, is essential. While inbreeding minimizes the genetic differences between animals, it also leads to an increase of the effect of the environmental component. Thus, inbred mice were found to be more variable in their response to estrogens than random-bred animals. For the purpose of good husbandry it is furthermore important to find the physiologically optimal conditions for the colony and then ensure a uniform supply of these conditions.

54. NICHOLS, J. E. The principles of animal production. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 3: 59–63, 1955.

Some principles applying to the breeding of farm animals are presented.

55. PERRY, J. S. Reproductive wastage. I. Pre-natal loss. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 3: 65–75, 1955.

Prenatal mortality in the rat, mouse, guinea pig, rabbit, cat and pig is discussed.

56. ROWLANDS, I. W. Reproductive wastage. II. Post-natal loss. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 3: 77–85, 1955.

Losses at parturition, neonatal mortality, and losses due to failure of lactation or conditions of rearing are reviewed.

57. STRONG, L. C. The origin of some inbred mice. II. Old techniques and new. *J. Natl. Cancer Inst.* 15: 1417–26 (Apr. Suppl.), 1955.

Three methods for the development of inbred strains of tumor mice are reported: *1)* Hybridization and selection; selection has been based upon the appearance of spontaneous tumors such as adenocarcinoma of the mammary, longevity, etc. *2)* Hybridization and selection followed for many generations by the injection of methylcholanthrene into breeding mice. *3)* Selection by starting with a relatively inbred or homozygous state and basing selection upon litter seriation or the age of parents at the time the offspring were born. (Condensed from author's summary)

58. TEMPLETON, G. S. *Domestic Rabbit Production.* Danville, Ill., Interstate, 1955, 210 pp.

Chapters are presented on the following topics: selection of breed and purchasing of stock; housing and feeding and watering equipment; marking; feeding; breeding; handling; quarantine and diagnosis of ailments.

59. CHARLES, R. T. The recording of inbred strains of mice used in cancer research. *J. Animal Technicians Assoc.* 7: 22–5 (June), 1956.

A system for the recording of breeding performance and spontaneous tumor incidence in cancer strains of mice is described.

60. CURRY, M. F. Weight changes of adults in an inbred colony of Syrian hamsters. *J. Heredity* 43: 302–4 (Nov.–Dec.), 1956.

The purpose of this work was to determine if 8 yr. of inbreeding, but not consistent brother-sister mating, had any undesirable effect on a colony of Syrian hamsters. It was found that in the 8-yr. period weights of the males increased an average of 25%, while the weights of the females neither increased nor decreased appreciably. At 140 days the average weight for 204 males was 17 gm heavier than the average weight for 260 females. Isolation at 35–40 days of age retarded growth in both sexes temporarily. No apparent undesirable effects were produced in the colony as a result of inbreeding. (Author's summary modified)

61. DETTMERS, A. Die Zucht eines neuen "Versuchstieres," des Miniaturschweines, in Amerika. (Development of a new experimental animal, the miniature pig, in U.S.A.) *Z. Tierzücht. Züchtungsbiol.* 68: 37–41, 1956.

The development of a miniature pig by the Hormel Institute is described.

62. FRAZER, J. F. D. Some aspects of the breeding of laboratory animals. *J. Animal Technicians Assoc.* 7: 31–4 (Sept.), 1956.

Based on a literature review it is apparent that in the various species of laboratory animals the effects of diet, light, cage size and composition of breeding groups have all to be considered as factors in the successful production of maximal numbers of young. This is apart from the question of the use of selected strains of animals where the number of ovulations per year, the number of ova per ovulation and the level of foetal and neonatal death are such as to make for the greatest number of young/100 females.

63. HARROP, A. E. Artificial insemination in dogs. The first transatlantic conception. *Brit. Vet. J.* 112: 338–40, 1956.

The techniques used in collecting, preserving and transporting canine semen from England to New York and insemination in New York 140 hr. later are described. Due to lack of estrus in 4 out of the 5 inseminated dogs, only one became pregnant producing after 66 days a litter of 5 healthy puppies.

64. LYON, M. F. Genetics and laboratory animal breeding. *J. Animal Technicians Assoc.* 7: 9–11 (June), 1956.

Principles of genetics and breeding are discussed.

65. NATIONAL RESEARCH COUNCIL, INSTITUTE OF ANIMAL RESOURCES. *Proceedings of Conference on the Production of Inbred Mice* (T. C. BYERLY, Chairman). Washington, D.C., Aug. 6, 1956, 42 pp.

The purpose of the conference was to provide a guide to producers and users of inbred mice. The following papers were presented and discussed: "Inbred mice: A program of accreditation and certification," by T. C. BYERLY; "Inbred mice: The needs of the Cancer Chemotherapy National Service Center," by K. ENDICOTT; "Inbred mice: Genetic aspects," by E. S. RUSSELL; "Inbred mice: Problems of mass production," by C. N. W. CUMMING.

66. POCKSON, A. P. The breeding and management of a small colony of ferrets. *J. Animal Technicians Assoc.* 7: 7–9 (June), 1956.

Handling, housing, feeding, reproduction and protection from diseases are discussed. Ferrets make a useful subject for the study of reproduction involving the additional use of artificial lighting.

67. WHITTEN, W. K. Modification of the oestrous cycle of the mouse by external stimuli associated with the male. *J. Endocrinol.* 13: 399–404 (July), 1956.

Mating of mice does not occur with equal frequency during the first 4 nights after pairing. Fewer than the expected number mate on the 1st, 2nd and 4th nights, but mating on the 3rd night greatly exceeds expectation. This effect is not dependent on age or parity and is little altered by pairing the mice at 11 P.M. when estrus behavior is fully established. Mating occurs more frequently on the 1st night after pairing if the male has been enclosed in a small basket within the female's cage for 2 days previously. Also, the incidence of mating is altered by placing the females in a cage recently contaminated by males. The estrus cycle of the mouse is apparently modified by the presence of a male or his excreta, and an exteroceptive stimulus functioning through one of the chemical senses is probably involved. (Author's summary)

68. CUMMING, C. N. W. AND ELIAS, C. The establishment by a commercial company of a colony of rats free from certain pathogens. *Proc. Animal Care Panel* 7: 41–9 (Mar.), 1957.

After experiments with a pilot colony which was free of intestinal parasites and pneumonitis, a new colony building accommodating 1200 breeders was erected. Heating, ventilation, cages, feeding and management are described in detail. Routine laboratory tests and gross and microscopic examination of all discarded breeders are employed to detect any disease which might appear and to maintain the colony free from pathogens.

69. HART, R. J. C. An outbreak of coccidiosis in laboratory rabbits. *J. Animal Technicians Assoc.* 7: 61–2 (Mar.), 1957.

Fresh green food should be fed only to rabbits used for breeding, and then only after it has been treated with ammonia; if a case of coccidiosis occurs, the feces of all rabbits in the colony should be examined for oocysts, and all excretors should be treated with sulphadimidine. Control measures, particularly ammonia treatment of cages and weekly examination of feces, should be continued for at least 6 wk. after the last evidence of infection. (Author's summary modified)

70. HENTHORNE, R. D. AND VEENSTRA, R. J. The development and maintenance of disease-free animal colonies at the Walter Reed Army Institute of Research. *Proc. Animal Care Panel* 7: 50–5 (Mar.), 1957.

The background leading to the establishment of the program of the Walter Reed Army Institute of Research and its achievements are reviewed. The disease-free colonies consist of 7 species of animals including 15 different strains, with a total monthly production of about 30,000 animals. Costs for mice at Walter Reed are about half that of current market quotation for commercial mice. (*See also* Abstract *4:* 82)

71. HORVÁTH, G. A kutya szülés elötti hömérséklet-változásainak diagnosztikai jelentöségéröl (On the diagnostic value of body temperature variations of the bitch before parturition.) *Magyar Állatorvosok Lapja* 12: 381–2 (Dec.), 1957.

Variations of the body temperature of 39 bitches were investigated before and after parturition. Such variations of the temperature before and during parturition were found to have great diagnostic and prognostic value. High (39°C) or very low (36.6°C) body temperatures before parturition indicate a complicated delivery and may be used as an indicator of the necessity of chemotherapeutic or surgical intervention. A high (39°–39.5°C) body temperature on the 1st or 2nd day after parturition indicates the necessity of an acceleration of the involution process.

72. INNES, J. R. M., DONATI, E. J., ROSS, M. A., STOUFER, R. M., YEVICH, P. P., WILSON, C. E., FARBER, J. F., PANKEVICIUS, J. A. AND DOWNING, T. O. Establishment of a rat colony free from chronic murine pneumonia. *Cornell Vet.* 47: 260–80 (Apr.), 1957.

A breeding colony of 11 paired matings was established out of 56 "Nelson" rats, 1–3 mo. old. Two to three litters were produced weekly from the original parents to a final total of 42 litters and 322 rats born. General health of the original parents and weaned rats was excellent throughout; the colonies were free from *Salmonella* and helminthic infections, bartonellosis, sarcosporidiosis, myocarditis, bacterial lung infections and chronic murine pneumonia.

73. LANE-PETTER, W. AND BLOOM, J. L. Control of genetic variation. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 6: 51–7, 1957.

Variation arises from genetic and environmental causes, that is, the variation may be genotypic or phenotypic. An inbred strain is nearly 100% homozygous; 2 inbred strains mated together will

be largely heterozygous. A closed population that is random mated, has less genetic similarity between its individual members than is found in inbred strains or their 1st crosses but more than an open or wild population. Factors influencing change within a population, such as genetic drift, are discussed.

74. LUNDBERG, W. O. Miniature pigs as experimental animals for medical and nutritional research. *Proc. Conf. on Research, Council on Research Am. Meat. Inst., Univ. Chicago* 9th Conf., Mar. 22–3, 1957, pp. 109–13.

A miniature pig was developed in the Hormel Institute by crossing wild guinea hogs from Alabama, the Piney Woods hog from Louisiana and a Catalina Island boar. Animals of the 5th generation had ⅕–½ the size of a normal pig; the final goal is a pig about ¼ the size of ordinary pigs. Miniature pigs are being used on studies of the fundamental causes of atherosclerosis.

75. MICHIE, D. "Superpregnancies" in mice. *J. Animal Technicians Assoc.* 8: 7–10 (June), 1957.

Artificial methods to increase the reproductive output of mice are discussed. Mice of the TO and M and B strain were injected with serum from pregnant mares and 42 hr. later with human chorionic gonadotrophin and then put overnight with males to mate. The frequencies with which mating and pregnancy were induced at various ages, the number of implantations found in the uteri of treated and control mice and post-implantation survival in M and B strain mice aged 38 days and over, were determined. The results showed that the average number of embryos could be doubled but there were abnormal losses at parturition.

76. NATIONAL RESEARCH COUNCIL, INSTITUTE OF LABORATORY ANIMAL RESOURCES, COMMITTEE ON STANDARDS (T. C. BYERLY, Chairman). Minimum standards for the commercial production of randombred and inbred laboratory mice. (Revised September 22, 1957) *J. Natl. Cancer Inst.* 19: 1137–43 (Dec.), 1957.

The article contains the following chapters: *1)* purpose and aim of the mouse producers accreditation program; *2)* to the user of laboratory mice; *3)* to the producer of laboratory mice; *4)* facilities and sanitation (caging and equipment, bedding, buildings, cleaning); *5)* disease diagnosis and prevention; *6)* genetics and record-keeping; *7)* nutrition.

77. NJAA, L. R., UTNE, F. AND BRAEKKAN, O. R. Effect of relative humidity on rat breeding and ringtail. *Nature* 180: 290–1 (Aug. 10), 1957.

Breeding difficulties of rats were overcome by maintaining the relative humidity in the breeding room above 50%. When pregnant rats were transferred experimentally to a room without humidity control, all young showed abnormalities of their tails 1 wk. after birth. It is suggested that the reason for the tail disorder at low relative humidity is due to a great heat loss from the naked newborn rat by evaporation.

78. REYNIERS, J. A. The control of contamination in colonies of laboratory animals by the use of germfree techniques. *Proc. Animal Care Panel* 7: 9–29 (Mar.), 1957.

Standards of laboratory animal colonies are discussed. Differences between germfree and clean animal colonies are explained. Methods of obtaining animals at the desired levels, their maintenance, diet, transportation and use in experiments are reviewed. Cesarean operation on a rat, using Reyniers Germfree System, and rearing germfree young by hand-feeding are described.

79. SHAPIRO, H. Breeding rabbits in small cages. *Proc. Animal Care Panel* 7: 138–41 (June), 1957.

A simple wooden nest box is described which permits breeding and raising young rabbits in small experimental cages. The box protects the young from drafts and cold and furnishes a means of mild exercise. Litters of 5–7 or more young have been accommodated in this size box and a number of adults have been reared and in turn used for breeding.

80. SHEFFY, B. E. Hand rearing of puppies. Paper presented at 7th Gaines Vet. Symposium, Kankakee, Ill., Oct. 23, 1957, pp. 9–11.

The method of hand-rearing puppies, in the absence of a bitch, is discussed.

81. SMITH, C. The introduction and breeding of the Chinese Striped hamster (*Cricetulus griseus*) in Great Britain. *J. Animal Technicians Assoc.* 7: 59–60 (Mar.), 1957.

Housing, feeding and breeding of the Chinese Striped hamster are described.

82. WALTER REED ARMY INSTITUTE OF RESEARCH, DIVISION OF VETERINARY MEDICINE. Establishment and maintenance of a disease-free animal colony. Washington, D.C., 1957, 15 pp.

A technique of raising disease-free, standardized laboratory animals has been developed. The following 3 areas were considered as the most important: *1)* housing, *2)* procurement and *3)* maintenance of the animals free of disease. Concerning housing, certain requirements of lighting, temperature, humidity and ventilation have to be met. To start a colony, disease-free animals may come from existing colonies or they may be obtained from selected stock by cesarean section. Once disease-free animals are obtained, they must be maintained in a disease-free environment whereby the following 4 primary sources of infection must be controlled: feed, bedding, equipment and the attendant. A colored motion picture "Animals in Research," which is a pictorial report on the establishment and maintenance of a desease-free animal colony, and a booklet, "Care and Management of Laboratory Animals," are available from the Division of Vet. Med., Walter Reed Army Inst. of Research, Walter Reed Army Med. Center, Washington 12, D.C. (See also Abstracts *4:* 70 and *5:* 123)

83. BACHARACH, A. L., CUTHBERTSON, W. F. J. AND FLYNN, G. W. The economics of laboratory animal breeding: Rats and mice. *Lab. Animals Centre, M.R.C. Lab., Collected Papers* 7: 31–43, 1958.

Management and size of breeding units for inbred strains of rats and mice and for hamsters are discussed. The mean number of square feet required by each unit and for necessary services in rat, mouse and hamster breeding colonies is reported. Building rates, insurance and equipment costs are tabulated. Labor hours and costs and cost of feed for the units are listed. In an appendix the composition of diets is given.

84. CLEMENTE, C. D. Studies on sexual behavior in cats and implications for the management of a breeding colony. *Proc. Animal Care Panel* 8: 20–2(Mar.), 1958.

The following important features of sexual behavior in the cat are relevant in the management of a breeding colony: *1)* Adaptation of the male to "territory" so that upon presentation of an estrous female, copulation can be expected immediately. *2)* Recognition of the estrous state in the female and presentation to the male only when this behavior is evident. *3)* Maintenance of adaptation in the male by presentation of behaviorally estrous females even if this necessitates spaying certain females and im-

planting pellets of female sex hormone. (Author's summary modified)

85. FOSTER, H. L. Large scale production of rats free of commonly occurring pathogens and parasites. *Proc. Animal Care Panel* 8: 92–100 (Sept.), 1958.

Details for the construction of animal facilities for the production of animals free of commonly occurring pathogens and parasites are described. The need of a rigidly controlled environment and the barriers necessary for insuring the exclusion of vermin and wild rodents are emphasized. The breeding cages are 24 x 24 x 9 in., 12 females and 3 males comprising a breeding unit.

86. FREUND, M. Collection and liquefaction of guinea pig semen. *Proc. Soc. Exptl. Biol. Med.* 98: 538–40 (July), 1958.

A method and an apparatus for routine electroejaculation of guinea pigs were developed, the semen coagulum or "vaginal plug" examined, and the coagulation process described. A series of proteolytic enzymes were tried for their liquefying activity and 0.1% chymotrypsin was found to result in consistent liquefaction and good sperm motility. Mean ejaculate volume was 0.5 ml and mean motility at 39°C was 51%. There was no evidence of gross morphological or histological changes in the reproductive system of guinea pigs electroejaculated at biweekly intervals (Author's summary)

87. GRAHAM, W. R. AND FEENSTRA, E. S. A program for the development of pathogen-free laboratory animals. *Proc. Animal Care Panel* 8: 54–66 (June), 1958.

The facilities (such as cages, sanitation, air conditioning) for development of pathogen-free colonies of laboratory animals are described. Procedures and methods used for cesarean section in mice and rats and hand-feeding of puppies and guinea pigs are given. An autoclavable diet was developed. Since autoclaving lowered the protein quality of the feed, 7% casein was added. The supplemented and autoclaved diet supported good growth and reproduction through 4 generations of rats.

88. GREGOIRE, A. T., BRATTON, R. W. AND FOOTE, R. H. Sperm output and fertility of rabbits ejaculated either once a week or once a day for forty-three weeks. *J. Animal Sci.* 17: 243–8 (Feb.), 1958.

Semen was collected with an artificial vagina from Dutch-type rabbits for a period of 13 wk. Following this 13-wk. preliminary period one group was ejaculated once each day and the other once each week for 43 additional weeks. There was no significant difference between average conception or average litter size for the does inseminated with sperm from bucks ejaculated once a week or once a day. Post-mortem weights and histological section of testes and adrenals revealed no signs of tissue damage. The study shows that rabbits may be ejaculated as frequently as once a day for as long as 10 mo. without impairing their libido, sperm production or fertility. (From author's summary)

89. HADEK, R. Intraperitoneal insemination of rabbit doe. *Proc. Soc. Exptl. Biol. Med.* 99: 39–40 (Oct.), 1958.

A technique for intraperitoneal insemination of rabbits is described. The results of the experiments showed that success of i.p. insemination is influenced by the time elapsed between ovulation and insemination and by the suspending media of the semen.

90. HANKIN, L. Filicidal cannibalism by female albino rats. *J. Nutrition* 66: 377–82 (Nov.), 1958.

Filicidal cannibalism occurred in rats maintained on Bills breeding diet. This diet is fed to animals bred to produce young which are used in bio-assays for vitamin D. The cannibalism caused by the apparently deficient Bills diet could be controlled by adding 3% whole liver powder to the ration but was not prevented by a 1% addition. Addition of 1% or 3% of whole liver powder also increased weaning weights of the progeny and did not impair the usefulness of the progeny for the vitamin D test.

91. KIDWELL, J. F. AND WEETH, H. J. Sex ratios and litter size in the laboratory rat. *J. Heredity* 49: 303–4 (Nov.-Dec.), 1958.

Sex ratio and litter size were studied among 1977 young from 222 litters. A significant effect of ration and a Ration × Generation effect on litter size was observed. There was no evidence of similar effect on sex ratio. There was no relation between litter size and sex ratio. (Condensed from author's summary)

92. KULEŠHOVA, V. G. (Influence of pH of diluted, stored rabbit semen on viability, fertilizing capacity and sex of offspring.) *Doklady Vsesoyuz. Akad. Sel'skokhoz- Nauk im. V. I. Lenina* 23: 40–4, 1958.

Rabbit semen diluted with a medium of glucose, citrate and egg yolk lived longest at pH 7–7.2 when stored at freezing point; it gave a high conception rate and a high viability of offspring. Storage at a more alkaline pH reduced fertility but increased size and weight of litters. Storage at a neutral pH resulted in a relatively greater number of female offspring, while storage at acid pH, apart from reducing the viability of the semen and the offspring, resulted in a relatively greater number of males in each litter. (*Vet. Bull.* 28: Abstr. No. 3040, 1958)

93. MACDONALD, I. Rearing of rabbits free from coccidal infection of the liver (*Eimeria stiedae*). *J. Animal Technicians Assoc.* 8: 68–70 (Dec.), 1957.

In order to obtain rabbits which had never had any infection with *Eimeria stiedae* it was found that segregation in separate quarters away from infected animals, feeding and watering before attending infected animals and the use of a saturated solution of nitrofurazone as drinking water could prevent coccidiosis in the liver. The original coccidia-free rabbits were obtained by heavy dosage of the doe during pregnancy and lactation with the nitrofurans and at weaning putting the young on the regimen above. (Author's conclusions)

94. MCLAREN, A. AND BIGGERS, J. D. Successful development and birth of mice cultivated *in vitro* as early embryos. *Nature* 182: 877–8 (Sept. 27), 1958.

An experiment was reported in which viable young were obtained from mouse embryos cultured for 2 days on a synthetic medium during an early stage of embryogenesis, using a culture technique based on that of Whitten. Immature female mice in which superovulation and mating had been induced by treatment with gonadotrophins were used as donors. The yield of live from cultured embryos did not differ significantly from the control yield.

95. REYNIERS, J. A. AND SACKSTEDER, M. R. Observations on the survival of germfree C3H mice and their resistance to a contaminated environment. *Proc. Animal Care Panel* 8: 41–53 (June), 1958.

Housing and feeding of a colony of germfree C3H mice is described. Germfree C3H mice will live for more than 600 days and breed through at least 7 generations. No tumors were observed in the germfree mice at 600 days. Death was caused (in

the following order): by *1*) metastatic calcification, *2*) fighting, *3*) volvulus due to enlarged cecum, *4*) unknown causes, *5*) accident. Conventional female C3H mice died of mammary cancer and males of hepatomas. When germfree C3H mice were exposed to a conventional environment (contamination), less than 15% survived for 48 hr.; the survivors adapted to the environment and bred into a colony. In contrast, germfree Swiss mice, under the same conditions, have a survival rate of about 80% and germfree rats of almost 100%. When exposed to a pure culture, e.g. *Microsporum epidermidis*, germfree C3H mice were less sensitive and none died during a 2-wk. observation period.

96. Ross, M. A., Wilson, C. E. and Gletfelty, D. R. Development of a disease-free rat colony with special reference to chronic respiratory diseases. *U.S. Army Chem. Warfare Labs. Technical Rept.* CWLR 2242, Sept. 1958, 24 pp.

This report covers what is termed phase I of the program to establish a colony of rats free of the pulmonary disease complex. Initial breeding stock was found to harbor the disease entity of otitis media in 11.8% of the animals; diagnosis was based upon gross examination and bacteriological culture procedures. Young stock from infected breeders were found to be grossly infected as early as 31 days of age which indicated that otitis is a more acute disease than generally believed. The methods of diagnosis, breeding practices, and care of colony are discussed. (*U.S. Govt. Research Repts.* 32: 679, 1959)

97. Rowlands, I. W. Insemination by intraperitoneal injection. *Proc. Soc. Study Fertility* 10: 150–7 (June), 1958.

The injection of spermatozoa into the peritoneal cavity of guinea pigs shortly after ovulation results in a very high conception rate. Although the time at which the eggs become fertilized is the same after i.p. insemination as it is after mating, it appears that the spermatozoa retain their fertilizing capacity for a shorter period after injection into the peritoneal cavity than after coitus. Only a very small proportion of fertilized eggs was recovered when whole semen was injected into the peritoneal cavity of rabbits at varying times. The injection of previously capacitated spermatozoa at about the time of ovulation is suggested as a means of increasing the fertilization rate. No success has yet been achieved in sheep.

98. Short, D. J. and Lamotte, J. The establishment of an experimental cat colony. *J. Animal Technicians Assoc.* 9: 3–6 (June), 1958.

Housing, feeding, reproduction and disease control are described. The estimated feed costs per cat were 1/7d/wk. (23¢/wk.) up to 26 wk. of age. The 2 main diseases of cats mentioned are feline infectious enteritis and feline pneumonitis.

99. Trexler, P. C. and Barry, E. D. Development of inexpensive germfree animal rearing equipment. *Proc. Animal Care Panel* 8: 75–7 (June), 1958.

An "isolator" consisting of a chamber for containing the sterile environment and a smaller double doored sterilizer or "sterile lock" for passing materials in and out of the sterile area without contamination is described for rearing germfree laboratory animals. The walls of the isolator may be built from flexible transparent plastic film or sheeting or from steel. The relative merits of the steel and the flexible plastic isolators are reviewed.

100. Andersen, A. C. and Parker, H. R. The production and use of beagles for radiobiological research. *Proc. Animal Care Panel* 9: 61–6 (June), 1959.

Production and maintenance colonies of beagles are discussed. Two dogs to each outside pen is the most practical and economical method for maintaining a large number. The pens are cleaned daily. One caretaker, on a 7-day basis is required for every 72 dogs. Proper nutrition and at least 10 sq. ft. of pen area per inch of body height for each dog should be provided. By feeding a diet containing meat, a lower incidence of disease and parasites and a higher mean level of erythrocytes are obtained. The dogs reared in this manner showed a consistently higher resistance to lethal doses of whole body x-irradiation.

101. Deringer, M. K. Occurrence of tumors, particularly mammary tumors, in agent-free strain C3HeB mice. *J. Natl. Cancer Inst.* 22: 995–1002 (May), 1959.

The development of tumors has been studied in mice of substrain C3HeB which was produced by transfer of fertilized ova from strain C3H to strain C57BL. Mammary tumors occurred in 4% of virgin females of substrain C3HeB at an average age of 20.7 mo., in 54.8% of breeding females at an average age of 19.2 mo., and in 74.4% of force-bred females at an average age of 17.9 mo. Mammary tumors occurred in 22.4% of C3HeB males, treated with diethylstilbestrol, at an average age of 15.0 mo. Hepatomas occurred more frequently in animals of substrain C3HeB than have been observed previously in any other inbred strain. They were found in 58.6% of virgin females at an average age of 24.1 mo., in 30.3% of breeding females at an average age of 21.0 mo., in 37.8% of force-bred females at an average age of 20.5 mo., in 55.1% of males, treated with diethylstilbestrol, at an average age of 23.3 mo., and in 90.5% of breeding males at an average age of 21.4 months. Ovarian tumors occurred frequently in the females of substrain C3HeB: in 47.5% of virgin females at an average age of 24.3 mo., in 37.4% of breeding females at an average age of 21.5 mo., and in 29.3% of force-bred females at an average of 21.6 months. (Author's summary)

102. Foster, H. L. A procedure for obtaining nucleus stock for a pathogen-free animal colony. *Proc. Animal Care Panel* 9: 135–42 (Dec.), 1959.

A surgical procedure which permits the establishment of pathogen-free and perhaps germfree nucleus stock is described. The method involves the removal of the intact uterus containing the fetuses and its transportation into a sterile plastic isolator which is maintained under positive pressure. Germfree fetuses can be delivered which can remain in the isolator for germfree rearing or for the establishment of a disease-free or pathogen-free colony.

103. Fuller, C. A. and Strong, L. C. Maternal age selection and the fertility of mice. *J. Gerontol.* 14: 156–8 (Apr.), 1959.

A statistical analysis of observations concerning the fertility of 826 mice belonging to 5 maternal age descents derived from a single outcross of a polydactylous mutant male to several C_{57} females is reported for the first 4 generations of inbreeding. The methodology used may be applicable to other breeding programs. (From author's summary)

104. Gustafsson, B. E. Lightweight stainless steel systems for rearing germfree animals. *Ann. N.Y. Acad Sci.* 78, Art. 1: 17–28 (May), 1959.

A large type of germfree rearing tank which can house 20–30 rats, and a smaller type for about 10 rats is described and illustrated. Both tanks are made of 2-mm thick stainless steel. The tanks are provided with sufficient food and water for a run of 2–3 wk. The composition of the stock diet is given. Rats have been reared in this equipment germfree and free from demonstrable virus in the feces up to the 7th generation. Growth and reproduction equal those in controls maintained on the same diet.

105. HENTHORNE, R. D AND KESTER, W. O. Disease-free laboratory animals as related to germfree life. *Ann. N.Y. Acad. Sci.* 78, Art. 1: 276–80 (May), 1959.

At present the terms "disease-free, pathogen-free, specific pathogen-free (SPF), cesarean derived and clean animals" are used interchangeably. Laboratory animal colonies are classified into the following 3 groups: *1*) germfree, *2*) disease-free and *3*) conventional whereby disease-free infers free of symptoms of disease, of latent infections and of the carrier status. Methods for the production of disease-free animals and their importance as research tools are discussed.

106. KIRK, R. W. Artificial insemination in the dog. *Allied Veterinarian* 30: 40–4 (Mar -Apr.), 1959.

A simple procedure for collecting and handling semen to avoid injuring sperm cells is described. Other factors which must be considered to assure maximum success also are discussed in some detail, including the examination of semen for motility and morphology, the influence of frequency of collection on fertility of semen, techniques for determining the time of ovulation and thus the correct time to inseminate, technique of insemination, and the storage, dilution and transport of semen. (Condensed from author's summary)

107. MENZIES, W. The effect of weaning age on weight gain in rabbits. *J. Animal Technicians Assoc.* 9: 59–61 (Mar.), 1959.

Litters of 30 does, selected at random from the breeding stock of about 100 does, were weaned at 4, 6 and 8 wk., respectively. All young were weighed weekly from age 4–16 wk. and the whole experiment was extended over 12 mo. to confound seasonal variation. The results of the study showed that under the prevailing conditions there was little difference in the weaning times with respect to weight reached at 16 wk. Rabbits weaned at 8 wk. were heavier at 8–11 wk. than those weaned at 4 or 6 wk. For rabbits being used at 16 wk. of age there seemed to be no advantage in weaning later than 4 wk. of age. This should allow a more efficient utilization of breeding does than that possible with later weaning.

108. MIYAKAWA, M. The Miyakawa remote-control germfree rearing unit. *Ann. N.Y. Acad. Sci.* 78, Art. 1: 37–46 (May), 1959.

A remote-control rearing unit for guinea pigs is described and illustrated. It permits the rearing of a greater number of animals than previously used equipment, and there is less possibility of contamination. A device is designed to prevent animals to escape from the mechanical hands.

109. NATIONAL RESEARCH COUNCIL, INSTITUTE OF LABORATORY ANIMAL RESOURCES, COMMITTEE ON STANDARDS (T. C. BYERLY, Chairman). Minimum standards for the commercial production of random-bred and inbred laboratory rats. *J. Natl. Cancer Inst.* 22: 869–76 (Apr.), 1959.

The following topics are discussed: Purpose and aim of the minimum standards for rat production; facilities and sanitation, including caging, cage sizes, bedding, feeding and watering devices; disease diagnosis and prevention; genetics and record keeping; nutrition. (*See also* Abstract *4:* 76)

110. NICOLL, C. S. AND MEITES, J. Prolongation of lactation in the rat by litter replacement. *Proc. Soc. Exptl. Biol. Med.* 101: 81–2 (May), 1959.

Lactation was prolonged in 16 Carworth and Long-Evans rats up to 70 days after parturition by replacing the litters every 10 days with an equal number of 4-day-old foster pups. Milk production, as judged by litter weight gains, declined about ⅓ after 1st 20 days and continued at this level for the remainder of 70-day period. (Condensed from author's summary)

111. PHILLIPS, B. P., WOLFE, P. A. AND GORDON, H. A. Studies on rearing the guinea pig germfree. *Ann. N.Y. Acad. Sci.* 78, Art. 1: 183–207 (May), 1959.

The rearing of the guinea pig germfree had been studied in experiments extending over a period of 5.5 yr. Numerous liquid, dry, and semisolid diets were devised and evaluated for their efficacy in sustaining life and promoting growth in germfree animals. The methodology evolved from the studies permits obtaining germfree guinea pigs of good quality and maintaining the animals in a state of good health to adult life. The survival time of the animals has been increased from a few days in the early trials to more than a year in the more recent experiments. Some limited information was obtained concerning the vitamin requirements of the germfree guinea pig. Certain anatomical and hematological characteristics of germfree guinea pigs are discussed. Authors were so far unable to rear germfree guinea pigs into the 2nd generation. (From author's summary)

112. REYNIERS, J. A. (Conference Chairman). Germfree vertebrates: Present status. *Ann. N.Y. Acad. Sci.* 78, Art. 1: 1–400 (May), 1959.

This series of papers relates to: *1*) instrumentation for rearing germfree vertebrates, *2*) rearing germfree vertebrates, *3*) characteristics of germfree and disease-free animals, *4*) use of germfree vertebrates in research and *5*) present status and future development of germfree life studies. The papers are abstracted individually.

113. REYNIERS, J. A. Design and operation of apparatus for rearing germfree animals. *Ann. N.Y. Acad. Sci.* 78, Art. 1: 47–79 (May), 1959.

The Reyniers Germfree System is made up of a number of individual units called isolators which can be used either separately or attached to each other to form multiple isolators. Basic and specialized germfree isolators are described and illustrated. Isolators, as well as food, water, bedding, and equipment, are sterilized *in situ*. A standard germfree isolator will house 14 jars of mice of 5 adults per jar, 28 adult rats, 8 adult Bantam or 4 standard breed chickens, or 10 adult guinea pigs. Mice and rats have been bred up to the 10th generation and held for more than 900 days; guinea pigs have been held for 14 mo. Costs for this germfree apparatus are comparable to any kind of germfree operation.

114. TREXLER, P. C. The use of plastics in the design of isolator systems. *Ann. N.Y. Acad. Sci.* 78, Art. 1: 29–35 (May), 1959.

Cold-sterilized plastic films may be used for isolators to rear, study and transport laboratory animals. Peracetic acid or β-propiolactone serves as a germicide. Plastic isolators have the advantage of being of lightweight and low in cost.

115. U.S. DEPARTMENT OF AGRICULTURE. Raising rabbits. *Farmers' Bull.* No. 2131, June, 1959, 48 pp.

Breeding, feeding and managing of rabbit colonies is discussed. The leaflet also contains chapters on sanitation and disease control and on record keeping. Illustrations accompany the text.

116 WHITTEN, W. K. Occurrence of anoestrous in mice caged in groups. *J. Endocrinol.* 18: 102–7 (Jan.), 1959.

When female mice were caged in groups of 30, regular estrus cycles did not occur in the majority of animals, but promptly

returned when the mice were caged individually. Also, regular estrus cycles did not occur in blind mice when grouped, or in normal mice separated by partitions in the cage. When grouped mice were subsequently paired, mating occurred 3 nights later in 53%. Anestrus in grouped mice is believed to result from a depression of pituitary gonadotropic function, independent of mutual visual or tactile stimuli. (The same data were published in *Nature* 180: 1436 (Dec. 21), 1957: Effect of exteroceptive factors on the eostrous cycle of mice.)

117. Wostmann, B. S. and Pleasants, J. R. Rearing of germfree rabbits. *Proc. Animal Care Panel* 9: 47–54 (June), 1959.

Germfree rabbits were obtained by Cesarean operation following the usual techniques. The baby rabbits which were fed a milk formula during the first 4 wk. showed no signs of nutritional deficiencies, with the exception of some loss of hair, and gained weight about ½–⅓ as fast as normal stock mother-fed rabbits. When weaned to sterilized solid food at the end of 4 wk., growth and general appearance were less satisfactory. All animals showed enlarged ceca and some developed muscular wasting and nephrotic symptoms. When the same sterilized solid diet was fed to normal stock rabbits, growth and general appearance were satisfactory. (Author's abstract)

118. Young, G. A., Underdahl, N. R., Sumption, L. J., Peo, E. R., Olsen, L. S., Kelley, G. W., Hudman, D. B., Caldwell, J. D. and Adams, C. H. Swine repopulation. I. Performance within a "disease-free" experiment station herd. *J. Am. Vet. Med. Assoc.* 134: 491–6 (June 1), 1959.

A "disease-free" swine herd was established by obtaining pigs by hysterectomy 1–3 days prematurely and raising them without colostrum in isolation for 4 weeks. These pigs were placed in a clean farm environment, without direct or indirect contact with other swine, raised to maturity, mated, and the next generations were farrowed normally and permitted to suckle their mothers. (From author's summary)

The following abstracts, although located elsewhere in this bibliography, are related to the subject of this section.

Section 1: 10, 15, 29, 35, 36, 39, 41, 45, 56, 61, 87, 110, 116, 123, 132, 135, 139, 140, 151, 152, 160, 162, 169, 177, 185, 203, 204, 209, 213, 220, 223, 227, 235, 236, 237, 241, 243, 245, 256, 259, 267, 272, 273, 274, 281, 288, 289, 293, 295, 296, 301, 303, 311, 312, 313, 316, 318, 320, 332, 334, 337, 342, 345, 348, 352, 353, 377, 384, 390, 393, 410, 431, 438, 444, 454, 465, 470, 481, 490, 511.

Section 2: 20, 21, 23, 26, 60, 62, 99, 101, 104, 108, 118, 122, 158, 168, 198, 254, 259, 264, 269, 274, 281, 282, 309, 327, 330, 353, 357, 358.

Section 3: 5, 11, 14, 15, 23, 36, 42, 43, 49, 51, 62, 71, 75, 83, 85, 87, 88, 91.

Section 5: 1, 9, 12, 17, 18, 19, 21, 27, 28, 29, 34, 38, 43, 46, 49, 54, 57, 63, 72, 78, 81, 90, 102, 106, 109, 110, 117, 123, 128, 129.

Section 6: 23, 26, 30.

Section 8: 1, 7, 9, 12.

Section 9: 2, 18.

5. Design and Operation of Maintenance and Use Colony[1]

1. Animal Welfare Institute. *Basic Care of Experimental Animals*. New York (no date), 36 pp.

The booklet deals with the needs of laboratory animals, disease prevention, parasites and skin troubles, cleaning and sterilization of equipment, humane ways of killing animals, and the care in the laboratory of rats, mice, guinea pigs, rabbits, dogs, cats, rhesus monkeys, poultry, amphibians, turtles and fish. Housing, bedding, feeding, environmental temperature and humidity, breeding, handling and marking are included in the discussion.

2. University of California, Committee on Animal Care. Recommendations for optimum caging and housing facilities for experimental animals. Republished by the Institute of Laboratory Animal Resources, mimeo (no date), 12 pp.

The routine housing, temperature and humidity requirements of dogs, monkeys, cats, rabbits, chicken, guinea pigs, rats, hamsters and mice are reported and recommendations for sanitary procedures are given.

3. Gross, L. and Connell, S. J. B. Separation of excreta from rats. *Proc. Physiol. Soc.* (Mar. 17), 1923, pp. lx–lxii.

A simple apparatus which automatically times and separates the excreta from rats is described and illustrated. The device consists of a cylindrical cage with a wire mesh bottom, resting on a large glass funnel.

4. Bliss, A. R. and Bliss, G. S. An improved animal cage for scientific investigations. *J. Lab. Clin. Med.* 14: 887–90 (May), 1929.

The cages described and illustrated may be built to any desired dimensions. They provide isolating compartments for different sizes of dogs, cats, rabbits, monkeys or other small animals and furnish maximum ventilation and visibility together with complete comfort to the caged animal.

5. Smith, A. H. and Brooke, R. O. A nonmetal cage for small animals. *Proc. Soc. Exptl. Biol. Med.* 28: 854–6 (June), 1931.

A cage consisting of a Pyrex cylinder resting on a grid made of galvanized iron is described and illustrated. A similar grid forms the top of the cage. Urine may drop through the bent tubes of the bottom grid. Food is provided in a glass cup which is connected to the upper grid; a water fountain is also supported from the collar of this grid. The cage is easily cleaned and sterilized and eliminates coprophagy.

6. Underhill, F. A., Orten, J. M. and Lewis, R. C. The inability of metals other than copper to supplement iron in curing the nutritional anemia of rats. *J. Biol. Chem.* 91: 13–25 (Apr.), 1931.

A glass cage for use in the study of the effects of metals in nutritional anemia of rats is described.

7. Bliss, A. R. An inexpensive but durable metabolic cage for small animals. *J. Lab. Clin. Med.* 18: 1076–7 (June), 1933.

A cage measuring 18 x 18 x 18 in., constructed of galvanized iron and hardware cloth, with a removable sliding bottom, is described and illustrated. Total weight is 18 lb. and total cost $18.50 per cage. The cages are large and strong enough for use in metabolic studies with small animals such as cats, adult rabbits and small dogs.

8. Nicholas, J. S. Savings in laboratory expenditures without loss of efficiency. *Science* 78: 38–9 (July 14), 1933.

Some economies are suggested which can reduce the costs on most colonies from 40%–60% without impairment of efficiency. Operating tables may be adapted from kitchenware, sterilization may be secured with a pressure cooker. Other suggestions are made concerning food and food equipment, caging, anesthesia, etc.

9. Blair, A. W. and Carmichael, E. B. Cage for mice and rats. *J. Lab. Clin. Med.* 19: 1020 (May), 1934.

The dimensions of the cage described and illustrated are 11.25 x 8.5 in. It is made of galvanized hardware cloth and consists of 2 compartments, permitting the segregation of bedding and food. It has been used for feeding experiments, breeding purposes, for stock animals and general experimental purposes.

10. Franke, K. W. and Franke, W. R. A metabolism cage for rats. *J. Lab. Clin. Med.* 19: 669–71 (Feb.), 1934.

A cage unit occupying a minimum of space, very easy to clean and very mobile (can be moved, to balance for the weighing of rats and food, or from room to room) is described.

11. Evans, F. L. A simple and inexpensive cage for mice. *J. Lab. Clin. Med.* 24: 1306–7 (Sept.), 1939.

A cage made of a tin can and fitted with a cover of hardware cloth is described. The can is placed in a wooden rack to keep it from rolling. A large hole admits the water tube. The device may be used for inoculation of animals or as a metabolism cage.

12. Main, R. J. *The Care of a Small Rat Colony*. St. Louis, Mosby, 1939, 101 pp.

In the 1st chapter on rooms, author discusses the space required for production and maintenance colonies and their temperature regulation. Chapter 2 on equipment deal with air conditioning, heating, ventilation, sanitation, bedding and feeding and watering utensils. Other chapters are concerned with cleaning and painting, rearing, mating and growth, feeding, economics, disease and vermin. A daily routine of certain important procedures in the operation of a production colony is given. Books on rats, their

[1] Arrangement is chronological by year of publication. A list of additional references, located in other sections of this bibliography, will be found on page 109.

feeds and equipment are listed. A chapter describing methods of assaying vitamin D by using rats, is included.

13. RAY, T. W. An all-glass adjustable mouse cage. *J. Lab. Clin. Med.* 25: 323–5 (Dec.), 1939.

The all-glass cage described provides ample ventilation, glass wheels for exercising, an attached fountain. It can easily be disassembled for cleaning and is convertible into 1, 2, 3 or 4 units.

14. BAUMGARTNER, L. L. Trapping, handling, and marking fox squirrels. *J. Wildlife Management* 4: 444–50 (Oct.), 1940.

A trap, a handling cage for squirrels, and procedures for marking are described. A source for bands is noted.

15. GREENE, R. L. A new model mouse cage. *J. Lab. Clin. Med.* 26: 701–2 (Jan.), 1941.

A cage and runway for optimum living conditions is illustrated. To save space, 16 units can be placed on a rack. Forty-eight cages on 3 racks, housing 250 mice, require a space of only 4 x 11 ft.

16. SELYE, H., BASSETT, L. AND NIELSEN, K. An improved rat cage for metabolism studies. *J. Lab. Clin. Med.* 26: 1849–51 (Aug.), 1941.

The cage described and illustrated has the following advantages: *1*) no contamination of feces and urine by food; *2*) no washing of feces by urine; *3*) extreme accuracy in measurement of food and water intake; *4*) minimum urine evaporation; *5*) low cost, unbreakability and rust resistance.

17. REYNIERS, J. A. Housing laboratory animals. *Modern Hosp.* 58: 64–7 (Mar.), 1942.

Diagrams are presented of *1*) service units for experimental animal laboratories, *2*) a combination of units essential to housing and experimenting on laboratory animals and *3*) isolation cages. *Diagram 2* is discussed in detail. The plan contains the following units: stock animal rooms for protecting breeding stock; storage rooms; ventilation traps at the entrance of any isolation room; sterilization room for washing and sterilizing cages; quarantine rooms; experimental units; contaminated materials room where food and other material brought from the outside is unpacked, sterilized and then stored; special rooms, such as machine shop, etc. Ventilation, air conditioning and temperature control are discussed. Construction and arrangement of cages are described.

18. REYNIERS, J. A. How to care for laboratory animals. *Modern Hosp.* 58: 62–3 (Apr.), 1942.

A floor plan of Notre Dame's research laboratories of bacteriology is illustrated and the step-by-step procedure of handling laboratory animals and their supplies in these laboratories is described. Incoming animals are deloused and then put in a quarantine laboratory for observation period. When they are ready for breeding they are moved into the stock animal quarters. Animals removed from the stock animal colony for any purpose are never returned to it. Records are kept for each animal. Handling of food and water supplies and cleaning and sterilization of cages are discussed.

19. FARRIS, E. J., CARNOCHAN, F. G., CUMMING, C. N. W., FARBER, S., HARTMAN, C. G., HUTT, F. B., LOOSLI, J. K., MILLS, C. A. AND RATCLIFFE, H. L. Animal Colony Maintenance. *Ann. N.Y. Acad. Sci.* 46, Art. 1: 1–126 (June), 1945.

The following papers were presented at the Conference on Animal Colony Maintenance held by the Section of Biology of the New York Academy of Science, Nov. 10–11, 1944: Genetic purity in animal colonies; mating of mammals; feeding laboratory animals; infectious diseases of laboratory animals; influence of environmental temperatures on warm-blooded animals; financing and budgeting, viewpoint of the University and viewpoint of the commercial breeder.

20. FISCHER, R. G. A device to facilitate the cleaning of cages containing cotton rats. *J. Lab. Clin. Med.* 33: 519–20 (Apr.), 1948.

A device is constructed which is dropped into the cage by sliding it under the lid as the lid is raised. The device with the rats under it can be lifted from the cage and the cage may then be easily cleaned and supplied with fresh bedding and food.

21. LITTLE, A. D., INC. Qualitative specifications for animal laboratories for experimental work with radioactive materials to Brookhaven National Laboratory. *U.S. Atomic Energy Comm.* AECU-298, Dec. 8, 1948, 94 pp.

Information pertinent to the construction of animal laboratories for radioactive experiments, including recommendations as to layout, materials of construction, technique of operation and precautionary measures, is presented. Receiving, quarantining, breeding, housing and maintenance of the animals are discussed. In the appendix, specific chapters deal with the albino rat (including tabulations of approximate body measurements at 4 stages of growth, colony room size, labor requirements), mouse, guinea pig, rabbit, dog; dimensions of cages are given for each species.

22. MUNKELT, F. H. Air purification and deodorization by use of activated carbon. *Refrig. Eng.* 56: 222 (Appl. Data 42: 1–8 (Sept.), 1948.

Assuming that 1 room of an animal laboratory houses 5000 rats and has a gross space of 20,000 cu. ft. or 4 cu. ft. per animal, the required total odor-free air to dilute to threshold is 7,500 cfm of which 20% or 1500 cfm should be outdoor air. This required total odor-free air volume is the equivalent of 22.5 turnovers/hr. which is about twice that ordinarily permissible without detriment to animal health. Average odor-free air requirements for dilution of odors to threshold concentration in animal laboratories are given as follows:

Animal	Weight	Heat Generation*	Gross Space	Odor-free Air
	gm	*Btu/hr.*	*cu. ft.*	cfm
White mice	21	0.6	1.0	0.10
Rats	200	3.6	3.5	0.75
Rats	400	5.5	4.0	1.5
Guinea pigs	410	5.7	6.0	1.5
	kg			
Rabbits	2.6	19.0	10.0	2.0
Cats	3.0	25.0	35.0	8.0
Monkeys	3.2	25.0	100.0	20.0
Dogs	14.0	80.0	150.0	50.0
Hen	2.1	19.0	8.0	2.0
Cock	2.8	24.0	8.0	2.0

Values given are average values per animal. * Btu values are for animals in muscular repose, 24 hr. after feeding.

23. HILL, J. W. Kennels and equipment. In: MCCAY, C. M. ed. *Nutrition of the Dog.* 2nd ed. Ithaca, N.Y., Comstock Pub. Associates, 1949, pp. 289–97.

Construction and equipment of dog kennels and special panel pens for puppies and smaller dogs are described and illustrated.

24. U.S. Public Health Service, National Institutes of Health, Surgery Study Section. Care of the dog used in medical research. *Public Health Reports* Supplement 211, 1949, 14 pp.

The following items of concern to the research worker are discussed: Public relations, procurement, housing, sanitation and feeding. The Michigan State Law, which makes it possible to procure dogs from public pounds, and a model city ordinance, which makes it possible to salvage dogs which would otherwise be killed, are presented.

25. American Animal Hospital Association, Hospital Building and Equipment Committee. *Planning Your Animal Hospital*. Skokie, Ill., Rogers Park Press, 1950, 155 pp.

A guide for building a convenient, safe and attractive hospital for small animals (cats and dogs) is presented. Chapters deal with: choice of a location, preliminary planning, floor plan, illustrations of various types of hospitals, architecture, materials, construction finishing, furnishing, financing.

26. Brewer, N. R. Dog cages for the research laboratory. *Proc. Animal Care Panel*, 1st Ann. Meeting, Nov. 28, 1950, pp. 28–34.

A storage cage, a metabolism cage and a convalescent cage for dogs are described and illustrated.

27. Farris, E. J. ed. *The Care and Breeding of Laboratory Animals*. New York, Wiley, 1950, 515 pp.

The book contains chapters on the monkey, rat, mouse, guinea pig, Syrian hamster, rabbit, dog, cat, ferret, opossum, fowl, reptiles, amphibia, fish as laboratory animals, *Drosophila*, as well as on control of pests and parasites in laboratory animals. For each animal, housing, maintenance, reproduction, nutrition, diseases, sanitation and transportation are discussed.

28. Herrlein, H. The care and housing of animals from a commercial breeder's viewpoint. *Proc. Animal Care Panel*, 1st Ann. Meeting, Nov. 28, 1950, pp. 2–9.

Guide lines are given for transportation and housing of mice, rats, guinea pigs and rabbits. Maintenance cages, for best results, should not accommodate more than 15–20 mice, 6–10 rats or 4–6 guinea pigs per unit; rabbits are best caged individually. Mice, rats, guinea pigs or rabbits should not be bedded on shredded sugar cane which, being edible, creates a degree of toxicity, though this type of bedding will be suitable for dogs, cats, poultry or farm animals. An adequate diet should be provided; any change of diet will temporarily affect mortality and growth rate. Ideal room temperatures for mice and rats are 72°–75° F, for guinea pigs 60°–65°, while rabbits do best outside. In the discussion the use of wood for breeding cages and of peat moss for bedding is pointed out; floors should be painted with a carbolineum-like product. (Sugar cane bedding is toxic only in the opinion of the author.)

29. Thorp, W. T. S. Facilities for medical research with animals. *Proc. Animal Care Panel*, 1st Ann. Meeting, Nov. 28, 1950, pp. 17–19.

A building program for animal houses for maintenance and production colonies is briefly sketched.

30. Bond, E. and Flynn, R. J. Standardization of animal care procedures. *Proc. Animal Care Panel*, 2nd Ann. Meeting, Nov. 29–30, 1951, pp. 89–99.

Cage material and size, number of animals per cage, daily cost, frequency of cage cleaning and sterilizing, man hours needed per wk. per 1000 animals are recorded for mice, rats, guinea pigs, rabbits and dogs.

31. Bruner, H. D. An expendable cage to separate the urine and feces of rats in tracer experiments. *U.S. Atomic Energy Comm. Doc.* ORO-5, 1951, 2 pp.

A rat cage constructed from ½-in. mesh galvanized hardware cloth, in which the urine falls through the floor to be absorbed on paper below and the feces roll down the sloping paper surfaces into an evaporating dish, is described and illustrated.

32. Hargreaves, C. C. The function of an animal supply department. *Proc. Animal Care Panel*, 2nd Ann. Meeting, Nov. 29–30, 1951, pp. 83–9.

Experience of Eli Lilly Co., scheduling of duties, and forms used are described.

33. Heidelberger, C. and Weiss, S. M. The distribution of radioactivity in mice following administration of 3,4-benzpyrene-5-C^{14} and 1,2,5,6-dibenzanthracene-9,10-C^{14}. *Cancer Research* 11: 885–91 (Nov.), 1951.

A restriction cage for mice, constructed from coarse wire screening, is described and illustrated. The animals could be maintained in this cage with adequate food and water for up to 21 days. By means of an attached collar the mice were prevented from licking the sites where carcinogen had been applied.

34. Young, W. A. Feline housing, restraint and medication. *Proc. Animal Care Panel*, 2nd Ann. Meeting, Nov. 29–30, 1951, pp. 2–18.

Basic psychology, habits and diet, breeding habits, restraint and handling, transportation, anesthesia and the following diseases and treatments are discussed: internal and external parasites, ear trouble, skin disease, wounds, dentistry, fractures, infectious and contagious diseases, surgery, laparotomies, spaying, castration, cryptorchids, cystitis and urethral calculi, foreign bodies, hair balls.

35. Anonymous. Industrial air conditioning. *Heating, Ventilating, Air Conditioning Guide* 30: 933–54, 1952.

For good air quality conditions the following space per animal and total air circulation (all outdoor or decontaminated air in recirculation) should be provided:

Animal	Space per Animal *cu. ft.*	Total Air Circulation *cfm*
Mice	3	0.5
Rats	4	0.75
Guinea pigs	6	1.9
Rabbits	10	1.9
Hamsters	8	1.5
Cats	35	10.0
Dogs	150	28.0

36. Brewer, N. R. Some problems in animal quarter construction in urban areas. *Proc. Animal Care Panel*, 3rd Ann. Meeting, Dec. 3–4, 1952, pp. 64–9.

Common deficiencies in the construction of animal quarters are discussed, such as too small entrance doors, insufficient drainage facilities, waterproofing and heating, etc.

37. Cohen, B. J. and Bond, E. Cage equipment for laboratory rats and mice. *Proc. Animal Care Panel*, 3rd Ann. Meeting, Dec. 3–4, 1952, pp. 107–19.

The relative advantages and disadvantages of various types of construction materials for rat and mouse cages, design, size and cleaning of the cages, feeding and watering equipment and costs are discussed.

38. CORNELIUS, O. The routine care of cats in the laboratory. *J. Animal Technicians Assoc.* 3: 41–2 (Sept.), 1952.

Housing, feeding, breeding and handling of cats is discussed.

39. FLYNN, R. J. Problems in the construction of animal quarters in surburban and rural areas. *Proc. Animal Care Panel*, 3rd Ann. Meeting, Dec. 3–4, 1952, pp. 47–63.

Two experimental animal quarters are described. One of the buildings was to be used primarily for a study of the effects of fast neutrons and gamma rays on mice. All animals were procured from commercial breeders. They were housed, 8 to a cage, in 7.5 x 11.5 in. plastic boxes which were air-conditioned to 74°F ± 4° with a relative humidity of 50% ± 10%, and fed commercial pellets. The 2nd building described was for general biologic and particularly radiobiologic research with various animals. Floor plans of both buildings are included.

40. FOLLETT, A. T. The procurement and management of guinea pigs for routine diagnosis. *J. Animal Technicians Assoc.* 3: 33–4 (Sept.), 1952.

Guinea pigs are used in large numbers to test either milks or material from tuberculous patients. Housing and feeding of these animals is described. The need of fresh green food in their diet is demonstrated, and their water requirement is discussed.

41. GUEST, G. M., BRODSKY, W. A. AND NELSON, N. Metabolism cage for rats, with feeding device that minimizes food scattering. *Metabolism* 1: 89–91 (Jan.), 1952.

A metabolism cage with glass sides, made from an inverted 3-gal. bottle with bottom removed, with coarse-mesh wire-screen floor and a fine-mesh screen below it, affords efficient separation and collection of urine and feces. A feeding device used in the cage (a diagram for which is given) minimizes the mixing of scattered food in the urine and feces, an important hazard in quantitative balance studies. (Author's summary)

42. HENRY, K. M. Metabolism cages for small laboratory animals. *J. Animal Technicians Assoc.* 3: 53–5 (Dec.), 1952.

A review is presented of the 2 most commonly used types of metabolic cages, those by Ackroyd and Hopkins and by Mitchell. A survey of cages designed for specific purposes is included.

43. ISAACSON, J. H. Mouse house management. *J. Animal Technicians Assoc.* 3: 37–8 (Sept.), 1952.

Housing, including temperature control, hygiene and breeding of mice, are discussed and the need of suitable personnel for management is pointed out.

44. PEREIRA, W. P. Housing and management of experimental animals. *J. Animal Technicians Assoc.* 3: 49–52 (Dec.), 1952.

The layout and construction of an experimental unit comprising soundproof kennels, animal house, operating theater, etc., are described together with notes on bedding, feeding and trapping of animals. (From author's summary)

45. RUDDY, J. M. Air conditioning rodent quarters. *Heating and Ventilating*, Mar., 1952, pp. 4–5.

When the new section of the Biology Laboratory in Brookhaven was built, data were collected for year-round air conditioning of the rodent quarters in order to establish the most satisfactory conditions for health and breeding of rats and mice. In winter, the temperature should be maintained at 80° ± 2° F with a possible drop to 75° for a period not exceeding 4 hr. on very cold days. In summer, the temperature should be kept at 72° ± 2° F with a permissible fluctuation between 72° and 78° for a period of not less than 3 hr. and not more than once in 1 day out of 4 consecutive days. The standard humidity of 50% ± 10% R.H. is satisfactory. Drafts must be avoided. An alarm system should announce immediately any failure of the system.

46. SACHS, W. B. *Praktische Tierpflege für Naturfreunde und Forscher.* (*Practical Animal Care for the Layman and Investigator.*) Stuttgart, Franckh, 1952, 106 pp.

Life history, breeding, maintenance and care of laboratory animals, as well as of animals used in their diet, are given briefly in encyclopedic style. The following animals are included: protozoa, sponges, coelenterates, anthozoa, worms, crustaceae, arachnids, insects, diptera, mollusks, cephalopods, echinodermates, fish, amphibia, reptiles, birds and mammals.

47. VAN BRUGGEN, J. T. Cage-hood assembly for small animals. *Nucleonics* 10: 64–6 (Mar.), 1952.

The cage-hood assembly was designed to minimize $C^{14}O_2$ hazards in experiments with small animals metabolizing C^{14} compounds. The double-tier arrangement accommodates 12 hood-type containers, each of which is vented by a duct system. Round funnel-bottom metabolism cages are set inside the boxes and may be replaced by conventional wire cages when urine and feces are not being collected. The model is illustrated.

48. ANONYMOUS. Consider the pre-fabricated kennel. *Gaines Dog Research Progr.* Spring, 1953, pp. 6–7.

Prefabricated kennels are described.

49. BIESTER, H. E. The use of poultry in the medical laboratory. *Proc. Animal Care Panel*, 4th Ann. Meeting, Dec. 2–3, 1953, pp. 98–105.

Procurement, housing, nutrition, diseases and genetics of poultry are discussed.

50. BREWER, N. R. Dog cages for the research laboratory. *Proc. Animal Care Panel*, 4th Ann Meeting, Dec. 2–3, 1953, pp. 189–91.

Four different types of dog cages are presented, the storage, metabolism, convalescent and the combination cage. Illustrations are included.

51. DICKMAN, S. R. A metabolic cage. *Science* 117: 284–5 (Mar. 13), 1953.

A cage constructed from a conic projection obtained from war surplus, was developed in order to demonstrate the tricarboxylic acid cycle and the subsequent electron transfer reactions. It is suggested that these cages could be readily constructed from wire baskets obtainable at nurseries.

52. DIETERICH, W. H. Cages for small laboratory animals. *Proc. Animal Care Panel*, 4th Ann. Meeting, Dec. 2–3, 1953, pp. 182–5.

Two cages are described which provide for the health and comfort of the animals, allow them to be fed and watered without the necessity of opening the doors, provide for their security and protection, can be easily cleaned, sterilized, stacked and stored, and are adaptable for a variety of uses.

53. FERGUSON, I. D. AND RAMSAY, A. G. An automatic refilling water container for laboratory animals. *J. Physiol. (London)* 121: 37P–9P (June), 1953.

A water unit working by gravity feed and containing a float valve similar to that in a carburetor is described. It is somewhat expensive and elaborate but allows the water intake of animals to be measured with some degree of accuracy.

54. FLYNN, R. J. Small animal cages. *Proc. Animal Care Panel*, 4th Ann. Meeting, Dec. 2–3, 1953, pp. 186–88.

Four different types of cages for rats and mice are described. The 1st three types are for usual laboratory studies while the 4th type may be used as a carrying, isolation, or special breeding cage or for bacteriological, or radioactive isotope studies.

55. HANSARD, S. L. A metabolism unit designed for radioisotope balance studies with dogs. *Science* 117: 301–2 (Mar. 20), 1953.

A metabolism unit using a circular false floor separator, on which the dog stands during the experimental period, is described. It has wide applications in studies involving radioisotopes and when it is desirable to make separate urine and fecal collections.

56. KAPLAN, H. M. The care and diseases of the frog. *Proc. Animal Care Panel*, 4th Ann. Meeting, Dec. 2–3, 1953, pp. 74–92.

Grass or leopard frogs (*Rana pipiens*) are used for pregnancy testing. Maintenance, nutrition and diseases of frogs in general are discussed. (43 references)

57. RALSTON PURINA COMPANY RESEARCH LABORATORIES. *The Care and Feeding of Laboratory Animals*. St. Louis, 1953, 28 pp.

Environment and housing, breeding, developing breeding stock, sanitation and nutrition and feeding directions are discussed for rats, mice, guinea pigs, rabbits, dogs, chickens, hamsters, cats, monkeys. Other chapters deal with: what to feed; ingredients in laboratory chow; chemical analysis of Purina chows; Purina laboratory chow, research laboratories, research farm, sanitation products and feeders.

58. SUMMER, W. Odor control with ultra-violet radiation. *Food Manuf.* 28: 230–5 (June), 1953.

Ultraviolet air deodorization equipment has been proved effective in such varied installations as slaughterhouses, hospitals, waste processing departments, pathological and industrial laboratories, refrigerated cargo vessels, kitchens, dining rooms, food plants, fertilizer plants, pharmaceutical plants, etc. The equipment is relatively inexpensive to install and can be operated on as little as 1200 watts per 24-hr. day.

59. THORP, W. T. S. Small animal cages. *Proc. Animal Care Panel*, 4th Ann. Meeting, Dec. 2–3, 1953, pp. 178–81.

Specifications are given for the construction and for finishing of stainless steel cages. Illustrations are included for maintenance and metabolism cages, plastic and metal "shoebox" type cages with interchangeable lid and for 2 types of animal room carts.

60. BEDFORD, T. Ventilating and heating of animal houses. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 2: 69–72, 1954.

Warm and fresh air requirements, methods of ventilation, and heating are discussed.

61. BENSON, R. E., FREMMING, B. D. AND YOUNG, R. J. Care and management of chimpanzees at the radiobiological laboratory of the University of Texas and the United States Air Force. *Proc. Animal Care Panel*, 5th Ann. Meeting, Dec. 1–2, 1954, pp. 27–36.

Techniques of restraint, quarantine, housing, nutrition and diseases are discussed.

62. COHEN, B. J. An adjustable rack for small animal cages. *Proc. Animal Care Panel*, 5th Ann. Meeting, Dec. 1–2, 1954, pp. 92–5.

A cage rack which is useful because of its flexibility and serviceability under a variety of caging situations, is described and illustrated.

63. CUMMING, C. N. W. Animal house design in the United States of America. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 2: 41–52, 1954.

Animal houses at the Rockefeller Institute, Ciba Pharmaceutical Products, Inc., New York University Medical School, Mount Sinai Hospital, and National Institutes of Health are described. Room space required in use and breeding colonies of mice, guinea pigs, rats and rabbits is calculated.

64. GRIST, N. R. A small animal house for virus work. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 2: 29–33, 1954.

The design of 2 separate, single-storied 8-ft. blocks under one roof, one "clean" and one "infected" is presented. This arrangement permits separation of infectious experimental animals from "clean" ones.

65. HEMMINGS, W. A. Some factors in planning a small animal house. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 2: 21–7, 1954.

Site, design, construction, heating, ventilation and equipment of small animal houses are discussed.

66. HESS, S. M., LAUG, E. P. AND FITZHUGH, O. G. Metabolism cage for small animals. *J. Lab. Clin. Med.* 43: 824–6 (May), 1954.

A metabolism cage which permits the separate collection of feces and urine from small animals is described.

67. KERKMANN, O. H. Operation of the monkey colony at Okatie Farms. *Proc. Animal Care Panel*, 5th Ann. Meeting, Dec. 1–2, 1954, pp. 22–6.

Sources of monkeys, their feeding, housing, sanitation and transportation are discussed.

68. LABORATORY ANIMALS BUREAU, M.R.C. LABORATORIES. *The Design of Animal Houses*. (*Collected Papers* vol. 2) London, 1954, 75 pp.

For abstracts see: Bedford, T.; Cumming, C. N. W.; Grist, N. R.; Hemmings, W. A.; Parkes, A. S.; Sabourdy, M.; Strange, N.; Weitz, B.

69. LAZAROW, A. Design and construction of metabolism cages. In: STEELE, J. M., ed. *Methods in Medical Research.* Vol. 6. Chicago, Yr. Bk. Pub., 1954, pp. 215–57.

Metabolism cages for rats, mice, dogs and monkeys are discussed. Special consideration is given to details of construction, cage maintenance, efficiency of cleaning and avoidance of contamination. The special problems concerned in measuring the intake of food or water and the output of urine, feces or CO_2 are treated separately.

70. MATHEWS, E. D. J. Notes on use of new materials for surfaces in animal houses. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 2: 73–5, 1954.

The use of plastics and glass is suggested for walls, ceilings and floors.

71. NAGY, R., MOUROMSEFF, G. AND RIXTON, F. H. Disinfecting air with sterilizing lamps. *Heating, Piping, Air Conditioning* 26: 82–7 (Apr.), 1954.

An inexpensive high-intensity ultraviolet lamp giving optimum output in air conditioning was developed. The sterilizing effect of this lamp was demonstrated experimentally.

72. PARKES, A. S. Modernizing the animal house. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 2: 7–10, 1954.

General guide lines concerning construction of animal houses for use and breeding colonies, equipment and nutrition are presented. Recommendations for an efficient ventilating system are made.

73. SABOURDY, M. A new French animal breeding station. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 2: 35–40, 1954.

The center described consists of 6 separate buildings, connected by a gallery. It comprises 4 animal houses, 1 administration building and 1 central building for food preparation and cage washing.

74. SHORT, D. J. Methods used for maintenance of laboratory animals by National Institute for Medical Research, Mill Hill, London, England. *Proc. Animal Care Panel*, 5th Ann. Meeting, Dec. 1–2, 1954, pp. 127–34.

The development of the National Institute for Medical Research in Mill Hill, London, is described and methods used to house and maintain the animals are shown in a film. In the discussion, questions of sanitation and quarantine are reviewed. A report on a course for animal technicians given by the Institute is included.

75. SLANETZ, C. A. *Care of Laboratory Animals.* New York, American Public Health Association, 1954, 32 pp.

This handbook is a simplified practical guide on the care of laboratory animals commonly used in research and diagnostic work, such as mice, rats, guinea pigs, rabbits, hamsters, cotton rats, ferrets, cats, dogs, monkeys, sheep, goats, domestic fowl and frogs. Cages, cage capacity and cleaning, bedding, ventilation, diets and food storage, as well as control of laboratory pests and parasites and of some laboratory diseases are discussed.

76. SMITH, J. K. Problems related to housing and care of animals in an industrial research laboratory. *Proc. Animal Care Panel*, 5th Ann. Meeting, Dec. 1–2, 1954, pp. 146–50.

Housing, feeding, and diseases of mice, rats, guinea pigs, rabbits, cats, dogs, monkeys and chickens are discussed.

77. STRANGE, N. Animal houses: Some aspects of the design, construction and layout. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 2: 53–68, 1954.

Detailed suggestions are made for the construction of animal houses. The following points are discussed: site, design, insulation, ventilation, humidity, cleaning, sanitation, size of rooms, wall finishes, cages and cage racks, etc.

78. WEITZ, B. A new small animal unit. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 2: 11–9, 1954.

Design and construction of service, experimental and infected animal houses are discussed in general. Special attention is given to the guinea pig-breeding and rabbit house. Five line drawings and 7 photographs are included.

79. COMAR, C. L. Facilities and handling of radioisotopes with animals and plants. In: *Radioisotopes in Biology and Agriculture.* New York, McGraw, 1955, Chapt. 4, pp. 114–57.

A summary of management practice in small-animal colonies is presented. Housing and handling of mice, rats, guinea pigs, rabbits, dogs, monkeys and chicks before and after administration of isotopes are discussed.

80. KINKEL, M. P. AND SCRIBNER, G. M. Mouse cages and spontaneous tumors. *Brit. J. Cancer* 9: 464–72 (Sept.), 1955.

The purpose of the study was to determine whether mice that spend their lives in plastic cages are different from mice that live in metal cages. CF No. 1 female mice were housed in stainless steel or in methylacrylate cages from about 40 days of age till death. The mice in the plastic cages had a higher total incidence of tumors of both the reticular tissues and mammary glands while the incidence of lung and other tumors was the same in the 2 populations.

81. KOCH, W. AND HEIM, G. Die Haltung und Zucht von Versuchstieren. (*Maintenance and Breeding of Laboratory Animals.*) Stuttgart, Enke, 1955, 108 pp.

Maintenance, breeding, feeding and pathology of all important laboratory animals is discussed.

82. MILLER, O. T., SCHMITT, R. F. AND PHILLIPS, G. B. Applications of germicidal ultraviolet in infectious disease laboratories. I. Sterilization of small volumes of air by ultraviolet irradiation. *Am. J. Public Health* 45: 1420–3 (Nov.), 1955.

A UV sterilizer is described which is capable of eliminating high concentrations of bacterial spores from air at a flow rate of 1 cubic foot per minute and high concentrations of vegetative cells at 10 cfm. The apparatus utilizes 4 G36T6 UV lamps enclosed in aluminum tubes. The advantages of UV treatment of contaminated air from aerated bacterial cultures and small aerosol chambers are indicated and maintenance procedures are given. It is suggested that the apparatus may be employed to sterilize small volumes of air containing infectious microorganisms. (Author's summary)

83. WELLS, W. F. *Airborne Contagion and Air Hygiene. An Ecological Study of Droplet Infections.* Cambridge, Mass., Harvard Univ. Press, 1955, 423 pp.

Airborne infection and its control by air disinfection are discussed in general and also with regard to animals.

84. ANIMAL CARE PANEL. *Principles of Animal Care. Outline of Course in General Sanitation.* (V. SCHWENTKER, Chairman.) Mimeo, Chicago, Nov. 29, 1956.

This is the first section of a series of lectures for the training of animal technicians. The following topics are discussed: principles of infectious disease; principles of sterilization and disinfection, by L. R. CHRISTENSEN; practical application of sanitation techniques, by W. H. STEINMETZ; control of special problems, by R. J. FLYNN.

85. ANIMAL WELFARE INSTITUTE. *Comfortable Quarters for Laboratory Animals.* Mimeo, New York, Oct., 1956.

Housing for monkeys, dogs, cats, guinea pigs, rabbits, rats, hamsters and mice is discussed. A number of floor plans, construction details of various facilities, illustrations of cages and feeding devices are included.

86. BAKER, A. H. AND WHITFIELD, F. G. S. The control of parasites and pests in animal houses and food stores. *J. Animal Technicians Assoc.* 7: 36–42 (Sept.), 1956.

The term "aerosol" is defined and the technique of the continuous-flow aerosol is described. The application of the "C-F" aerosol for pest control in enclosed spaces is described with particular reference to animal parasites. The use of a bactericidal C-F aerosol for the control of airborne disease is discussed. Insecticidal U-F lacquers are described and their use in combination with C-F aerosol is discussed. The use of the C-F aerosol and the U-F lacquer for the control of stored products' pests is also discussed. (Author's summary)

87. BREWER, N. R. Why decentralization of animal quarters fits our needs at the University of Chicago. *Purina Lab. Animal Bull.*, Spring, 1956.

Use of laboratory animals in various research programs is described. The advantages of decentralization of animal units are pointed out.

88. DAVIS, J. A general account of insects and mites which infest laboratory animal feeding stuffs; their control and eradication. *J. Animal Technicians Assoc.* 7: 12–4 (June), 1956.

The following insects and mites infesting animal feeding stuffs are described: *Lepidoptera* (moths), *Coleoptera* (beetles), *Orthoptera* (cockroaches), and *Acarina* (mites). Preventive measures and control are discussed.

89. FENDRICK, A. J. How laboratory animals fit into the scheme of things at Smith, Kline and French. *Purina Lab. Animal Bull.* Fall, 1956.

Treatment of disease, housing, use of laboratory animals and training of personnel is discussed.

90. FLYNN, R. J. *Curso teorico practico de crianza de animales de laboratorio y prevencion de sus enfermedades.* (*Practical Course in the Care of Laboratory Animals and Prevention of their Diseases.*) Mexico, D. F., 1956, mimeographed copy.

The course includes directions on care and handling, reproduction and genetics, nutrition, cages and housing, diseases (bacterial, viral, fungal, parasitic, neoplasms, nutritional, etc., as well as diseases transferable to man), personnel, regulations, antivivisection. Animals included are rats, mice, guinea pigs, hamsters, rabbits, poultry, monkeys.

91. SCHWENTKER, V. Optimum cage sizes for rats. Symposium, Animal Care Panel, Chicago, 1956.

Since overcrowding may lead to chronic respiratory disease in mature rats and a decreased growth rate in growing rats, the optimum size of cages is an important question. Recommendations for optimum housing and caging were prepared in 1948 by the firm of Arthur D. Little, Inc., and in 1953 and 1956 by the University of California; a mathematical formula for calculating cage sizes was offered by Dr. Lane-Petter of the Laboratory Animals Bureau of England.

92. WEDUM, A. G., HANEL, E., JR. AND PHILLIPS, G. B. Ultraviolet sterilization in microbiological laboratories. *Public Health Repts. (U.S.)* 71: 331–6 (Apr.), 1956.

Ultraviolet radiation can be used around doorways and in airlocks to separate areas of unequal infectious risk and to reduce the number of infectious microorganisms and general contaminants in laboratories and in walk-in incubators. (Author's summary)

93. ADAMS, S. S. A method of housing stock or experimental guinea pigs. *J. Animal Technicians Assoc.* 8: 64–5 (Dec.), 1957.

A method of housing experimental guinea pigs in old-fashioned galvanized metal tubs is recommended, particularly for buildings which are not temperature controlled or where drafts are prevalent. The galvanized iron baths can be bought in hardware stores at a cost of about 50s. The floor dimensions are 16 × 51 in., but the sides, which are 11.5 in. high, slant outward to make the dimensions at the top of the bath 20 × 57 in. Attached to the top rim at each end is a substantial handle. Twelve to 20 guinea pigs, according to size, are kept in each bath on sawdust; the tubs are cleaned out 3 times weekly. A 1,000-ml water bottle, with the standard metal nozzle, is suspended in a wire cage. A leather luggage-label holder, containing the label, is strapped on to one of the handles. Animals are fed on pelleted Diet 18 and hay; cabbage is added 3 times weekly. The baths are stored in two tiers on Dexion racking. In order to economize on space, 3 tiers are contemplated. Animals remained in extremely good health and showed a low mortality rate.

94. ANIMAL CARE PANEL. Isolated ideas concerning the design of animal quarters. Part of a discussion presented at Animal Care Panel, Saturday, Nov. 9, 1957.

Housing, feeding and management of animal colonies is discussed.

95. BOURSNELL, J. C. AND GLEESON-WHITE, M. H. Temporary preservation of carcasses of small laboratory animals containing radioactive isotopes. *Nature* 179: 54 (Jan. 5), 1957.

A procedure has been worked out for the preservation of whole carcasses or portions of tissue of animals not greater than 3 kg in weight by sealing them in polyethylene bags together with a mixture of fresh bleaching powder and "Vermiculite" (a commercial expanded mica). By using this method carcasses containing short-lived isotopes can be preserved until the radioactivity is reduced to relatively innocuous levels before incineration and the task of collecting and disposing of the radioactive ash can be avoided.

96. GAY, W. I. Husbandry practices for the quarantining and conditioning of sub-human primates. *Proc. Animal Care Panel* 7: 83–8 (June), 1957.

XUM

A system of housing, feeding, shipping, quarantining and marking monkeys is described. Techniques for administering drugs, exposure and blood sampling techniques and sanitation are discussed.

97. HOYLAND, F. The care and use of guinea pigs in a Public Health laboratory. *J. Animal Technicians Assoc.* 8: 20–3 (June), 1957.

The use of guinea pigs for tests for the presence of *Mycobacterium tuberculosis* and for the pathogenicity of organisms is described. Caging, feeding, sanitation and disease control of the animal colonies are discussed.

98. HUDSON, R. G. A multiple housing unit for small mammals. *Turtox News* 35: 235 (Oct.), 1957.

A multiple housing unit for hamsters, mice and rats is described.

99. KAPLAN, H. M. The care and diseases of laboratory turtles. *Proc. Animal Care Panel* 7: 259–72 (Dec.), 1957.

Care and feeding of turtles and dietary, fungous, algal, bacterial, virus, tumor, protozoan, helminth and arthropod diseases are discussed.

100. PERKINS, F. T. AND SHORT, D. J. A new technique in the sterilisation of animal houses racking and cages. *J. Animal Technicians Assoc.* 8: 10–17 (June), 1957.

A new technique for the sterilization of animal rooms, is described. The technique involves a new ampholytic surface-active bactericide, Tego MHG, which is applied by a specially designed apparatus which delivers a 1% solution through a spray-lance. *In vitro* tests confirmed that Tego MHG possesses powerful bactericidal properties. Treatment of animal rooms, racks, cages, food hoppers, drinking bottles and spouts with hot 1% Tego MHG effectively sterilized the articles. After treatment with Tego MHG a thin wax-like bactericidal film remained on the surface of the articles which so far (6 mo.) has shown no toxicity for animals. (Author's summary)

101. PHILLIPS, G. B., REITMAN, M., MULLICAN, C. L. AND GARDNER, G. D., JR. Applications of germicidal ultraviolet in infectious disease laboratories. III. The use of ultraviolet barriers on animal cage racks. *Proc. Animal Care Panel* 7: 235–44 (Dec.), 1957.

A method for attaching ultraviolet lamps to animal cage racks is described. The ultraviolet barrier effectively reduced the number of airborne vegetative organisms which escaped from contaminated animals. The ultraviolet barrier prevented cross contamination from aerosols of vegetative bacteria produced in adjoining cages. Ultraviolet used in this manner was only partly effective against bacterial spores. Personnel working in rooms with ultraviolet cage racks must wear skin and eye protection. (Author's summary modified)

102. WORDEN, A. N. AND LANE-PETTER, W., ed. *The U.F.A.W. Handbook on the Care and Management of Laboratory Animals.* 2nd ed. London, Universities Federation for Animal Welfare, 1957, 951 pp.

Part I of this book deals with general considerations common to all problems. Legal protection of laboratory animals; animal house; animal house equipment; principles of hygiene and epizootiology; pests of the animal house; breeding methods: genetic considerations, economic considerations; nutrition of laboratory animals; handling laboratory animals; stock-recording systems; anesthesia and euthanasia; choice of the experimental animal; need for new laboratory animals; animal technician; Laboratory Animals Bureau; laboratory animal business in the U.S.A. Part II deals with individual species or groups of species broadly subdivided into the following classifications: rodents and lagomorphs; insectivores; carnivores; ungulates; primates; marsupials; birds; reptiles, amphibia and fish; invertebrates. The essential considerations treated in Part I are discussed in greater detail and specifically for animals most commonly used in laboratories. Their more common diseases, treatment and prevention, are also included.

103. WORDEN, A. N. AND WATERHOUSE, C. E. A metabolism cage for use with cats. *J. Animal Technicians Assoc.* 8: 66–7 (Dec.), 1957.

A diagram accompanies a description of this cage, which differs from the dog cage described by the authors (*ibid.* 7: 49–9, 1956) in its tubular heaters, weighing facilities, feedbox, rest shelves and water holder.

104. YOUNG, R. J., FLEMMING, B. D., BENSON, R. E. AND HARRIS, M. D. Care and management of a *Macaca mulatta* monkey colony. *Proc. Animal Care Panel* 7: 67–82, (June), 1957.

A maintenance colony of monkeys is described. Methods of diagnosis, control and therapy for bacterial, protozoan, helminthic and mycotic infections are reported. It is pointed out that adequate diet and sanitation are the most important factors for a successful colony management.

105. ANONYMOUS. Germ-free laboratory. *Science* 128: 1563 (Dec. 19), 1958.

A new and simplified germfree and virus-proof laboratory consisting of a sealed metal and glass box about the size of a deep-freeze cabinet, has been developed. By means of an attached pressure compartment, sterilization of food and equipment is possible. Contamination has been prevented in the new unit for more than 4 mo.

106. BARNETT, S. A. Laboratory methods for behaviour studies of wild rats. *J. Animal Technicians Assoc.* 9: 6–14 (June), 1958.

Methods for the maintenance, handling, photography and breeding of wild rats (*Rattus L.*) are described, with relevant information about the biology of *R. norvegicus* Berkenhout, the common 'brown' rat. (Author's summary)

107. CAMPBELL, D. A compact cage arrangement for study of individual diuresis in large numbers of rats. *Acta Pharmacol. Toxicol.* 14: 13–9 (Sept.), 1957–58.

A cage arrangement wholly of metal has been developed that not only gives good urine collection under physiological conditions but is also easy to make and needs little attention. The device allows quantitative collection of urine and feces individually from 50 rats on a table not more than 6 ft. long.

108. CASS, J. Some adaptive and pathological changes in laboratory animals associated with factors in their environment. *Proc. Animal Care Panel* 8: 13–9 (Mar.), 1958.

Various physical, chemical and biological agents in the environment which bear upon normal responses in the laboratory animal are discussed. Such factors as light, temperature, humidity, ventilation, housing space, sounds and odors as well as microorganisms and parasites are reviewed. Examples from the literature are given.

109. CUMMING, C. N. W. Report on meeting held at the New York Academy of Sciences concerning specific-pathogen-free animals. *Proc. Animal Care Panel* 8: 84–9 (June), 1958.

Differences between specific-pathogen-free (SPF) and non-SPF rats and mice in experimental work are discussed. Under most conditions SPF animals are hardier and more resistant to stress. Two methods of managing SPF colonies are outlined. In the first method, the cages are cleaned outside the animal room and returned there under sterile conditions. The second method uses the enclosed system by creating a barrier around a group. Personnel precautions in maintaining the barrier are described. Production costs, sterilization of feeds, nutrition and shipping are reviewed.

110. CUOZZO, R. F. 4-H rabbit raising handbook. *Maine Extension Service Bull.* 461: 1–20 (Jan.), 1958.

Housing, feeding, breeding, sanitation and record keeping are discussed.

111. DARMADY, E. M., HUGHES, K. E. A. AND JONES, J. D. Thermal death-time of spores in dry heat in relation to sterilisation of instruments and syringes. *Lancet* 2: 766–9 (Oct. 11), 1958.

In 1472 experiments the thermal death-times of *Clostridium tetani*, dried soil, and *Bacillus stearothermophilus* have been determined at temperatures ranging from 150° to 190°C. New standards for sterilization by dry heat are proposed. The safety margin will be adequate if the articles to be sterilized are kept at the sterilizing temperature for 1½ times as long as is necessary to kill all spores of *Cl. tetani* at a temperature 10°C lower. (Condensed from author's summary)

112. DARMADY, E. M., HUGHES, K. E. A., JONES, J. AND TUKE, W. Sterilisation by conducted heat. *Lancet* 2: 769–70 (Oct. 11), 1958.

For the small user a thermostatically controlled aluminium block, with holes which take syringes in their containers, is a reliable means of sterilization. Cutting instruments can be sterilized by laying them in a covered tray placed on top of the block. With the block maintained, as recommended, at 190°C, syringes should be heated for 18 min. and instruments for 30. If the block is started from cold, syringes will need 30 min. and instruments 45. (Author's summary)

113. DEOME, K. B. AND BARNAWELL, E. B. The economics of animal colony operation. *Proc. Animal Care Panel* 8: 113–27 (Sept.), 1958.

Building and equipment designs, based on a time-cost study of an inbred mouse production colony over a 6-yr. period are reported. Twenty-six illustrations are included showing floor plan of the Cancer Research Genetics Laboratory colony, arrangement of cages, various manipulations, etc.

114. EASTERDAY, O. D. AND SCHLOSSER, C. A modified experimental mouse cage. *J. Animal Technicians Assoc.* 8: 83–4 (Mar.), 1958.

A modified mouse cage has been described which permits a large degree of flexibility depending upon the immediate requirement. This cage design allows for greater convenience and decreased time expenditure in animal care. The cage does not rust or tarnish and allows for cleaning and sterilization with ease. (Author's summary)

115. FLYNN, R. J. Argonne National Laboratory animal facilities. *Lab. Animals Centre, M.R.C. Lab., Collected Papers* 7: 57–62, 1958.

The animal quarters in the Argonne National Laboratory are described and illustrated. Organization and responsibilities of the personnel and research studies on diseases and care of laboratory animals are reported.

116. FOLK, G. E. AND FOLK, M. A. A disposable isolation cage for hamsters and small mammals. *J. Animal Technicians Assoc.* 9: 53–5 (Dec.), 1958.

Economical and disposable cages made partly from discarded material, for use in long-term studies of rodents, are described and illustrated. Cost and source of water bottle are given.

117. HERRLEIN, H. G. *A Practical Guide on the Care of Laboratory Animals.* Decatur, Ill., A. E. Staley Mfg. Co., 1958, 45 pp.

The book discusses housing (including construction of cages, bedding, ventilation and environmental temperature), feeding equipment, vermin control, nutrition and disease of mice, rats, dogs, guinea pigs, rabbits, monkeys, cats, hamsters. A code of animal care for the caretaker concerning cleaning, bedding, feeding, handling and treatment of incoming animals is set up. Data of gestation period, estrous cycle, average duration of heat period, minimum breeding age and daily food consumption of the animals given above are tabulated. (56 references)

118. KINSEL, G. V. *The Theory and Practice of Nutria Ranching.* Toronto, Fur Trade Journal, 1958, 231 pp.

Care and raising, feeding and diseases of nutria are discussed. The review of the book in the *Journal of the American Veterinary Medical Association* (134: 481 (May), 1959) is not favorable.

119. KNODT, C. B. Private quarters for calves have many advantages. *Modern Vet. Practice* 29: 60–1 (Dec. 15), 1958.

It is claimed that isolation housing of the newborn calf will develop a hardy antibody system and achieve better general health. A complete "Calfloo" unit suitable for this purpose is described. The entire cost of the material used per unit will average less than $50.00 in most areas.

120. LACK, C. H., MICHIELI, R. AND NEWMAN, B. J. Saving labour in the animal house. *J. Animal Technicians Assoc.* 8: 81–2 (Mar.), 1958.

Cages for guinea pigs or rabbits with an automatic flushing mechanism operating from a 3-gal. cistern are described. For a battery of guinea pigs, flushing at 10-min. intervals is desirable whereas once in ½ hr. is sufficient for rabbits. In new animal houses detachable flat sections are used instead of cages which results in economy of space and easier sterilization.

121. RABSTEIN, M. M. The practical establishment and maintenance of *Salmonella*-free mouse colonies. *Proc. Animal Care Panel* 8: 67–74 (June), 1958.

Routine measures for the everyday handling of the colonies are listed. By applying the procedures described a *Salmonella*-free mouse colony was established and maintained without expenditure of a prohibitive sum of money.

122. SCHWENTKER, V. Housing for experimental animals. The West Foundation, mimeo (1954–58), 38 pp.

Planning, construction, air conditioning, lighting and sanitation of animal houses are discussed. Routine housing, temperature and humidity requirements are listed for dogs, monkeys, cats, rabbits, chickens, guinea pigs, rats, hamsters and mice.

123. U.S. Departments of the Army and Air Force. *Care and Management of Laboratory Animals.* (*U.S. Dept. Army Tech. Bull. Med.* 255; *U.S. Dept. Air Force Pamphlet* 160–12–3) May, 1958, 112 pp.

The material is arranged under the following main headings: Housing; cages; feeding and watering devices; bedding material; feed; sanitation—controlling transmission of disease; breeding programs; procuring and quarantining of laboratory animals; forms and records; personnel management (including an organization chart). Appendixes include: a bibliography of 116 references; space and production estimates; approximate cage space per adult animal; comparison of bedding materials commonly used for laboratory animals; sample feed formulas; breeding data; standard operating procedures for fabricating latex nipples, bacteriologic screening of breeding stock, monogamous matings of rats, mice, and guinea pigs, polygamous matings of rats and mice, colony mating of guinea pigs, colony mating of rats and mice, rabbit breeding, pregnancy determination in rabbits; sample specifications for purchase requests; common diseases of laboratory animals; common parasites of laboratory animals; standard operating procedures for management of purchased rabbits, examining animals for parasites, test for tuberculosis in primates, care of newly purchased young chimpanzees. Throughout the book, emphasis is laid on the prevention of disease and on the development of uniform, disease-free animals. Many illustrations are included.

124. Volf, V. (A cage for metabolic experiments with radioactive substances in rats.) *Physiol. Bohemosloven.* 7: 216–20, 1958 (in Russian).

A modification of the glass metabolic cage designed by Roth is described. Changes consist in the way in which air is introduced through the water screen and the possibility of cleaning the cage without opening it. The food container is adapted for administration of the standard Larsen diet. Urine and stool separator is partially coated with silicone. (From *Sci. Repts. on Ind. Hyg. and Occupational Diseases in Czechoslovakia* 3: 95, 1959)

125. Weiss, C. Care of guinea pigs used in clinical and research laboratories. *Am. J. Clin. Pathol.* 29: 49–53 (J1958.

Housing cages, quarantining, sanitation, diet, bacterial, protozoan, viral and metazoan diseases and personnel questions are discussed. Publications, books, films and journal references concerning the care of guinea pigs and sources of supply are listed.

126. Anonymous. Animal quarters design consultation. *Bull. Med. Research* 13: 9, 20 (Sept.-Oct.), 1959.

Announcement is made that the National Society of Medical Research is maintaining a clearing house for information on the design of laboratory animal quarters.

127. Anonymous. Paint that cuts noise. *Dog World,* June, 1959, p. 6.

Of particular interest to owners of kennels—especially kennels located in well populated areas—is a new paint that is said to help reduce the noise level in a building. Tests made in New York showed that noise in rooms painted with the new product was 25% to 33% less than in rooms that had coats of conventional paint. Its ability to absorb sound is attributed to the porosity and softness of the paint film, and the manufacturer states that the sound control is still effective after 2 yr. A single coat is claimed to provide effective sound conditioning, though a second coat may be added if additional sound control is desired.

128. Brooks, M. B. Care and management of opossums: Their use in pediatric research. *Proc. Animal Care Panel* 9: 167–72 (Dec.), 1959.

The care and management of maintenance and production colonies of opossums is described. It is similar to that of minks,

129. Foster, H. L. Housing of disease-free vertebrates. *Ann. N. Y. Acad. Sci.* 78, Art. 1: 80–88 (May), 1959.

A basic construction of masonry and steel with nonporous interior surfaces is a primary prerequisite. A minimum number of doors and no windows helps to exclude wild rodents and vermin. Air conditioning with bacterial filtration must be provided. A barrier system is used whereby everything within the unit or entering it is sterilized. Dimensions are listed for galvanized and stainless steel cages for maintenance and breeding. The procedures used for the sterilization of bedding and feed, removal of soiled bedding and excrement, and the watering system are described. Personnel must exercise strict precautions.

130. Horstman, V. G., George, L. A., Kerr, M. E. and Bustad, L. K. Miniature pig metabolism cage for radiobiological studies. *Proc. Animal Care Panel* 9: 181–2 (Dec.), 1959.

A cage for metabolism studies in miniature pigs was constructed of a stainless steel frame with Plexiglas sides. It has been used successfully with alpha-emitting isotopes. The cage is decontaminated before each metabolism study by spraying with a polyvinyl butyral dispersion.

131. Shechmeister, I. L. Disposable animal housing. *Information on Lab. Animals for Research, National Research Council* 3: 8 (Oct.), 1959.

Animal cages, particularly for mice, were fabricated from clear thermoplastic so that the entire cage or part of it was disposable. A new feeding and watering system was introduced. The cages were designed in a large size, with an area of 54 sq. in., for 6–8 adult mice, and a smaller size for single occupancy for 2–3 animals.

132. Southwick, C. H. Laboratory facilities for small mammals. *Turtox News* 37: No. 2 and 3 (Feb., Mar.), 1959.

Confinement facilities for mice, rats, guinea pigs and similar small laboratory animals are discussed. For routine maintenance of large numbers of animals battery cage systems offer the most efficient method of housing. Battery cages are expensive, drafty and require daily care. Laboratories with more modest means use unit cages. Minimum reasonable space requirements per individual are as follows: mice, no less than 15 sq. in.; rats, no less than 40 sq. in.; guinea pigs, no less than 50 sq. in.; rabbits, no less than 300 sq. in. (assuming a body weight of 2–3 lb.). Typical floor sizes for mouse cages are 9 x 7 in., 9 x 12 in. and 9 x 16 in. for 2, 3 or 4 mice, respectively. Feeding and watering equipment is discussed.

133. Whitten, H. Care and feeding of amphibians and small reptiles in the laboratory. *Proc. Animal Care Panel* 9: 85–92 (June), 1959.

Instructions on care and feeding are given for lizards, turtles, snakes, alligators, frogs, toads, newts, salamanders, *Necturus maculosus* and *amphiumae.*

134. YOUNG, F. A. A living-cage design to simplify the care and handling of monkeys. *Proc. Animal Care Panel* 9: 173–80 (Dec.), 1959.

An expanded-metal cage with a squeeze-type back and removable floor and automatic water system is described and illustrated. Fifteen cages are combined to a unit. The unit has been in use for 1 yr. with an average of 45 min/day devoted to the care of 15 animals by graduate assistants.

THE FOLLOWING ABSTRACTS, although located elsewhere in this bibliography, are related to the subject of this section.

Section 1: 13, 39, 41, 44, 87, 101, 135, 144, 160, 175, 196, 203, 204, 265, 307, 311, 327, 379, 403, 414, 416, 422.

Section 2: 26, 29, 30, 31, 32, 36, 44, 45, 53, 69, 70, 74, 97, 105, 116, 117, 122, 124, 135, 168, 214, 219, 246, 268, 274, 280, 295, 309, 317, 319, 331, 362, 368.

Section 3: 2, 3, 7, 16, 17, 33, 50, 62, 84.

Section 4: 2, 5, 6, 7, 10, 13, 14, 23, 38, 45, 49, 58, 66, 68, 70, 76, 78, 81, 87, 95, 98, 99, 100, 104, 106, 109, 112, 114, 115.

Section 6: 15, 16, 22, 37, 41.

Section 7: 31, 60, 61, 84, 160, 172.

Section 8: 1, 7, 12.

Section 9: 9, 10, 18.

6. Procurement and Use of Animals[1]

Including Marking of Animals, Standards, Legislation, Transportation, Quarantine

1. McCay, C. M. Interstate shipment of dogs. *Practical Doggery* 1, No. 2, 4 pp. (no date)

General regulations and those applying specifically to the individual states are discussed.

2. McAlpine, U. L. A simple and efficient method for permanently numbering rabbits. *J. Lab. Clin. Med.* 14: 891–2 (May), 1929.

A device for tattooing numbers on the inner surface of the rabbit's ear is described. The numbers are permanent; no infections have been observed.

3. Hutt, F. B. Research with a hen. *Science* 78: 449–52 (Nov. 17), 1933.

A review of the uses of the hen in animal experimentation is presented.

4. McClendon, J. F. and Street, H. Homozygous mice as biochemical test animals. *J. Biol. Chem.* 109: lxi–lxii (Proc.) (Apr. 10–13), 1935.

The use of mice as biochemical test animals is desirable when only small amounts of the test substance are available. Variability of growth is less the more homozygous the breed of mice is in regard to genes influencing growth. Bagg albinos have proved useful in testing vitamins, hormones and amino acids.

5. Varney, P. L. A device for permanently marking laboratory animals. *Science* 82: 46 (July 12), 1935.

A simple and inexpensive machine is described. Tattooing is considered the best method of marking laboratory animals such as rabbits and monkeys.

6. Walker, G. A method of numbering laboratory rats. *Science* 82: 397–8 (Oct. 25), 1935.

The toes of the hind feet are taken as units and the toes of the forefeet as 10's. Holes and punches in ears designate 100's and 1000's; 10,000 is made by clipping tails. The system has been used for a colony of 13,000 and was found satisfactory.

7. Beach, F. A., Jr. A new method for marking small laboratory animals. *Science* 87: 420 (May 6), 1938.

A simple and practical method of marking rats is to tattoo the identification numbers in the ear with India ink. Young rats can thus be marked for life at the time of weaning.

8. Carmichael, E. B. A system for numbering laboratory animals. *Science* 87: 557–8 (June 17), 1938.

Laboratory animals may be marked by notches, holes, and slits in the ears, clipped toes and clipped tails. Notches made by scissors in the right ear are taken as units and notches in the left ear as tens. The notches give a continued sequence from 1 to 99.

9. Dohan, J. S. A numerical system using colors for marking albino rats and mice. *J. Lab. Clin. Med.* 25: 872–4 (May), 1940.

By using 1–4 colors on 1–4 of 9 locations on the animal, about 5,500 different combinations are available and may be designated numerically.

10. Mitchell, P. C. Regulation of experiments on living animals. *Nature* 149: 699 (June 20), 1942.

At the end of June the Home Office will make an appointment under the Cruelty to Animals Act, 1876, which regulates the practice of experiments on living animals. An inspector under the Act will advise research workers in the interpretation of particular cases.

11. Anderson, R. C., Henderson, F. G. and Chen, K. K. The rat as a suitable animal for the study of prolonged medication. *J. Am. Pharm. Assoc., Sci. Ed.* 32: 204–8 (Aug.), 1943.

The rat is proposed as the testing animal for the study of prolonged medication. Certain advantages are pointed out, and examples with 12 products are given. (Author's summary)

12. Mangold, W. S. The University of California's sanitation service code. University of California rules regarding animals. *Proc. Animal Care Panel*, 1st Ann. Meeting, Nov. 28, 1950, pp. 34–9.

Rules concerning the purchase of domestic animals and their use for research purposes are published. A warning regarding dog or other animal bites is given.

13. Schlotthauer, C. F. Procurement of animals. *Proc. Animal Care Panel*, 1st Ann. Meeting, Nov. 28, 1950, pp. 20–5.

Procurement of dogs and cats from pounds and owners is discussed.

14. Bürki, F. Der Goldhamster als Versuchstier in der mikrobiologischen Laboratoriumspraxis. (The golden hamster, an experimental animal for microbiological laboratory practice.) *Z. Hyg. Infektionskrankh.* 133: 160–8 (Aug.), 1951.

The golden hamster is suitable for tests with anaerobic bacteria (*Clostridium chauvoei, C. novyi, C. gigas, C. welchii, C. histolyticum*), virulent *B. anthracis* and fixed rabies virus, but unsuitable for the diagnosis of *B. tuberculosis* and erysipelas; *Pasteurella, Salmonella,*

[1] Arrangement is chronological by year of publication. A list of additional references, located in other sections of this bibliography, will be found on page 115.

Brucella, *Streptococci pyogenes* and *Trypanosoma*. The maintenance of hamsters in the laboratory is complicated by their tendency to be necrophagous. Furthermore, they do not lend themselves to i.v. or intracardiac injections and therefore are unsuitable for experiments which require daily bleeding.

15. ANIMAL CARE PANEL, ANIMAL CARE STANDARDS COMMITTEE. Standards for the care of the dog used in medical research. *Proc. Animal Care Panel*, 3rd Ann. Meeting, Dec. 3–4, 1952, pp. 123–6.

A set of standards was drawn up concerning personnel responsible for the care of dogs and physical facilities.

16. MCDIARMID, A. Some aspects of research on brucellosis. *J. Animal Technicians Assoc.* 3: 21–3 (June), 1952.

The design of housing cattle for brucellosis immunity experiments is shown, and the methods used for testing *Br. abortus* vaccines, including the use of guinea pigs, is discussed. It is possible to differentiate between strains of *Br. abortus* by their particular degree of virulence for the guinea pig.

17. NATIONAL RESEARCH COUNCIL, AGRICULTURAL BOARD (W. J. LOEFFEL, Chairman). *Laws, Rules, and Regulations Governing Animal Health in the United States. A survey of measures in effect in 1946.* Mimeo, 123 pp., 17 tables, 1952.

The development of regulatory measures, state organization for the control of animal disease, regulation of livestock movement and sales, sanitation and hygiene and other pertinent material are presented. The livestock includes cattle, hogs, sheep and goats, horses, mules, asses, dogs, poultry, wild and semiwild animals. States where health certificates are required for incoming dogs are listed, together with state regulations concerning vaccination of dogs for rabies.

18 COOK, D. L., CALVIN, L. D. AND KALM, M. A. The use of the cat in the bioassay of choleretic agents. *J. Pharmacol. Exptl. Therap.* 109: 167–74 (Oct.), 1953.

A simple 5-hr. assay for choleretic agents using dehydrocholic acid as the standard and the cat as test animal is described. The assay is based on the increase in bile volume (ml/cat) during a 4-hr. collection period above the expected control for the same period. Sex difference had no apparent influence. The method is applicable to a variety of synthetic organic compounds.

19. EATON, O. N. Coordinating efforts in the development of animal resources. *Proc. Animal Care Panel*, 4th Ann. Meeting, Dec. 2–3, 1953, pp. 169–72.

The history of the organization of the Institute of Animal Resources within the Division of Biology and Agriculture of the National Research Council is described. The purposes of the Institute are given as follows: *1*) To survey and put on record the existing sources of production and supply of animal material used in biological, medical, and cultural research, assay, and testing. *2*) To coordinate and organize this information in such a way that it can and will be available for distribution to individuals and institutions engaged in such assay, testing, and research. *3*) To develop and establish reasonably scientific standards for the production, nutrition, hygiene and shipment of such animals. *4*) To take such steps as may be necessary to preserve the continuation of the various genetic strains or stocks of such material now available, or to be available, or to be developed in the future. *5*) To study the need for such material, both under peacetime conditions, and in the event of a possible national emergency, and to take steps to organize and have in readiness the personnel and other facilities for such extension of activity as may be necessary. (From author's summary)

20. EDITORIAL: Dogs for research. *J. Am. Med. Assoc.* 151: 914–5 (Mar. 14), 1953.

Bill HR 216 which was introduced into Congress is discussed. This Bill would transfer the functions of the poundmaster of the District of Columbia to private organizations which might well include antivivisection agencies. The National Society for Medical Research, in discussing the bill, calls it unnecessary and an insidious and insulting blow at medical research.

21. EVANS, S. A small animal carrier. *J. Am. Vet. Med. Assoc.* 123: 225 (Sept.), 1953.

A washable carrier which can be rolled up for compactness, for carrying and transporting of sick or dead dogs and cats, is described.

22. FRIMMER, M. Technik des pharmakologischen Tierexperimentes bei Verwendung radioaktiver Isotope. (Techniques in pharmacological animal experimentation when radioactive isotopes are used.) *Angew. Chem.* 65: 126–31, 1953.

The study deals with selection and care of animals, administration of isotopes, excretion of tracer substances, determination of isotopic concentration in blood and organs, studies with C^{14}, dosage of radioactive isotopes in animal experimentation and radiological damage.

23. GOWEN, J. W. Selection of appropriate animal material for a given investigation. *Proc. Animal Care Panel*, 4th Ann. Meeting, Dec. 2–3, 1953, pp. 151–62.

The following topics are discussed: selection of species; selection within species; inbred lines: identical twins; hybrids between long inbred lines; double matings; F_2 family progenies; tracer technique; selecting pathogens; recognizing mutant possibilities.

24. HOAG, W. G., GOCHENOUR, W. S., JR., AND YAGER, R. H. Use of baby chicks for isolation of leptospires. *Proc. Soc. Exptl. Biol. Med.* 83: 712–3 (Aug.–Sept.), 1953.

Two-day-old chicks uniformly developed leptospiremia persisting for at least 5 days following i.p. inoculation of leptospires. The organisms could be recovered from heart's blood cultures but could not consistently be demonstrated in cultures of either kidney or liver emulsions. No clinically detected illness resulted from the infection nor was there constant significant serologically demonstrable antibody response. Employment of chicks for recovery of leptospires from materials contaminated with other microorganisms and hence unsuitable for direct culture is suggested.

25. LANE-PETTER, W. Animal experimentation in Great Britain. *Proc. Animal Care Panel*, 4th Ann. Meeting, Dec. 2–3, 1953, pp. 115–29.

In the course of 1952 some 2,000,000 animals (mice, rats, guinea pigs, rabbits, hamsters, dogs, cats, ferrets, monkeys, chickens, pigeons, amphibia) were used in some 600 laboratories throughout the country. The development and the work of the Laboratory Animals Bureau in Great Britain, the laws governing experimentation with animals and the establishment of accredited sources of animals are discussed.

26. LANE-PETTER, W. The supply of laboratory animals. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 1: 7–23, 1953.

The numbers, cost and quality of different species of laboratory animals used in Great Britain, such as mice, rats, guinea pigs, rabbits, amphibia, cats, dogs and monkeys, are reported. The relative merits of breeding and buying animals and other factors concerned with obtaining them are discussed. Four problems are given particular attention: the provision of inbred strains, of infection-free animals, the supply of cats and dogs, and the importation of primates.

27. CALIFORNIA (State). Laws and regulations relating to care of laboratory animals. Excerpts from the *California Health and Safety Code* (Div. 2, Chapter 5, Sect. 1650–1677, Incl.) and California Administrative Code (Title 17, Chapter 2, Subchapter 1, Group 5), 1954.

Laws and regulations referring to general provisions, administration and regulation, application of the chapter, offenses against the chapter, revenue, certification requirements and minimum standards are published.

28. FULLER, J. L. AND SCOTT, J. P. Genetic factors affecting intelligence. I. Heredity and learning ability in infrahuman mammals. *Eugenics Quart.* 1: 28–43 (Mar.), 1954.

Experimental methods for the study on the inheritance of behavior patterns in dogs are reported. The use of animals in psychogenetic studies is pointed out.

29. FULTON, G. P., MAYNARD, F. L. AND WEST, G. B. Tissue mast cells in the hamster. *J. Physiol. (London)* 124: 29–30P (Mar.), 1954.

The use of the cheek pouch of the Syrian hamster for the study of the small blood vessels is pointed out.

30. GOWEN, J. W. Significance and utilization of animal individuality in disease research. *J. Natl. Cancer Inst.* 15: 555–72 (Dec.), 1954.

The following problems are discussed: selection of species; selection within species; inbreeding as a means of differentiating and purifying types within a population; inheritance in disease resistance; the cellular dependence of individuality in natural resistance to mouse typhoid; biological characteristics of significance to resistance and susceptibility; humoral elements in individuality of disease resistance; cellular elements in individuality of disease resistance; individuality of the genotypes for resistance to different diseases; individuality of the agent initiating the disease; individuality of the host and pathogen in acquired immunity.

31. MORGAN, C. F. The procurement of animals in the District of Columbia. *Proc. Animal Care Panel*, 5th Ann. Meeting, Dec. 1–2, 1954, pp. 116–8.

In 1954 the commissioners of the District of Columbia by executive order made impounded animals available to approved institutions after previous inspection of the animal quarters to be used. An animal allocation board was created and strict rules for housing and sanitation were set up. These safeguards proved satisfactory to the people who previously had opposed animal experimentation. (*See also* Abstract *6:* 45)

32. SMITH, D. C. Baltimore's dog ordinance after five years' experience. *Proc. Animal Care Panel*, 5th Ann. Meeting, Dec. 1–2, 1954, pp. 119–24.

Baltimore's dog ordinance became effective in January 1950. Since that time the City Animal Shelter has been turning over to properly authorized medical research institutions dogs for experimental use which otherwise would be killed in the shelter's gas chamber. The ordinance specifies the type of institutions entitled to receive unclaimed strays and lays down certain rules for their care. A proposed amendment prohibiting the burning over of impounded dogs to medical schools was defeated at a general election by a vote of 4.2 to 1. The fact that individuals voluntarily surrender their dogs to the Shelter is another indication of the public's acceptance of the use of impounded dogs for medical research. An advertisement of the Maryland Anti-Vivisectionist Society in 1954 against this use had no effect on public opinion. The ordinance has been entirely satisfactory.

33. SOAVE, O. A. The California animal care law. *Proc. Animal Care Panel*, 5th Ann. Meeting, Dec. 1–2, 1954, pp. 110–5.

The Animal Care Law, as passed by the California State legislative body in July 1952, states that "The Public Health and Welfare depend upon the humane use of animals for scientific advancement in the diagnosis and treatment of human and animal diseases, for education, for research in the advancement of veterinary, dental, medical, and biologic sciences, for research in human and animal nutrition, and improvement and standardization of laboratory procedures for biologic products, pharmaceuticals, and drugs." With the passage of the law the position of an Assistant Public Health Veterinarian and of a secretary in the Department of Public Health were created. Regulations were drafted which were embodied into the Health and Safety Code. These regulations require that all persons using or keeping animals be certified by the Health Department, that their animal quarters be inspected, that records be kept of the animals used and that certain standards in respect to care, housing, feeding, sanitation and handling personnel be maintained.

34. ALEXANDER, B. F., MUELLER, L. F. AND NICK, R. T. Guinea pig as a test animal for pyrogenicity. *Federation Proc.* 14: Abstr. No. 1012 (Mar.), 1955.

To determine the utility of the guinea pig as an assay animal for routine detection of pyrogens, comparative data were obtained for the guinea pig and rabbit regarding dosage response, tolerance and reaction to pyrogenic and nonpyrogenic solutions. Guinea pigs were found to be more sensitive to Piromen (standardized pyrogen) than rabbits and to be more consistently sensitive. An intravenous dose of 3 ml/kg in the guinea pig gave the same magnitude of response as 10 ml/kg in the rabbit.

35. ANIMAL WELFARE INSTITUTE. Transportation of monkeys by air. *Information Report* 4, No. 4, (Sept.–Oct.), 1955.

Regulations for handling and shipping monkeys, proposed by the British Medical Research Council and endorsed by one of the largest importers of monkeys to the U.S., are presented. The adoption of these regulations by all importers of monkeys is urged.

36. MACCARTHY, A. Proposed rules for care of laboratory animals. *Natl. Soc. Med. Research* 10: 13 (Mar.–Apr.), 1956.

The rules proposed by the president of the Anne Arundel County Society for the Prevention of Cruelty to Animals, Maryland, and printed on an advertisement page of the Bull. of the N.S.M.R. refer to handling, minimal housing and sanitation of laboratory animals.

37. CHANCE, M. R. A. The contribution of environment to uniformity. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 6: 59–73, 1957.

In the 1st part, on variance control, the physiological response to environmental changes is discussed. Based on a paper by Chen, K. K. *et al.* (*J. Pharmacol.* 79: 127, 1943), the effects of temperature (20°–40°C) in mice on potency of insulin, strychnine sulfate, aconitine hydrobromide, tutin and picrotoxin and the variability in response of the injected animal are tabulated. In another table the results of a study by the author on the effect of temperature on the toxicity of amphetamine, methedrine and ephedrine are listed.

In the 2d part, on refinement in pharmacology, uncontrollable variance in bioassay procedures and methods by which responses to environmental stimuli can be stabilized are discussed.

38. COHEN, B. J. AND CHALBERG, C. A simple ear punch for use on laboratory rats. *Am. J. Vet. Research* 18: 687 (July), 1957.

A snipe-nosed plier made of tempered steel is described. Using this tool, as many as 4 holes or notches can be made in each ear and many hundreds of rats can be numbered serially. Presumably, the same instrument can be used for mice.

39. JENKINS, D. W. Laboratory animals. *Science* 125: 753 (Apr. 19), 1957.

Under the auspices of the International Union of Biological Sciences, UNESCO, and the Council for International Organizations of Medical Sciences, an International Committee on Laboratory Animals was established in December, 1956. The aims of the committee are to ensure adequate supplies of uniformly high-quality laboratory animals. A world list of strains of laboratory animals is being compiled and a documentation center will be established. A report on the customs, quarantine and other regulations concerning international shipments of laboratory animals will be prepared.

40. LANE-PETTER, W. The utilization of laboratory animals in Great Britain. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 6: 11–7, 1957.

Proportionate distribution of the 5 main species used in the laboratory (mice, guinea pigs, rabbits, rats and chicken) and the purposes for which they are used are reviewed. A diagram lists the sources of these 5 main species, i.e. dealers and laboratories. Mortality of laboratory animals from natural causes and incidence of myxomatosis in dogs and cats are presented graphically.

41. SLANETZ, C. A. AND FRATTA, I. Stress and transportation of animals. *Proc. Animal Care Panel* 7: 278–89 (Dec.), 1957.

Stress related to shipment of mice, rats and guinea pigs by rail or motor vehicle is minimal during the cool and cold seasons of the year. CWL stock guinea pigs tolerate high humidity and high temperatures much better than rats or mice, but weight loss occurs in all 3 species. A large number of rats and mice died during transit in summer and showed an increase of lung pathology. Outdoor housing is compared to indoor housing. The results of the transportation experiments are tabulated.

42. STEWART, R. J. C.: The dog's place in medical research. *J. Animal Technicians Assoc.* 8: 31–5 (Sept.), 1957.

A review pointing out the usefulness of the dog in medical research, especially in the field of nutrition. Among the applications cited is that of the discovery that canine hysteria was due to the agene treatment of flour.

43. ANONYMOUS. Désinfection des wagons servant aux transports des animaux. (Disinfection of railway cars used for transport of livestock.) *Bull. offic. epiz.* 49: 304, 1958.

For the disinfection of railway cars the International Union of Railways (France) recommends the spraying of floors and walls before, and twice after removal of litter, with a 1% solution of commercial formol at the rate of 30–40 l/car. The solution should be used at 50°C, which increases its disinfectant properties and reduces the time for the smell of formal to disappear.

44. CUMMINGS, C. N. W. Sales problems of the laboratory animal supplier. *Proc. Animal Care Panel* 8: 34–6 (Mar.) 1958.

Laboratory animal suppliers consist of breeders and dealers. The industry is operated on the laws of supply and demand. The breeder must keep accurate records of his production and sales. Because of inescapable fluctuation in production, a breeder should not commit more than 90% of his estimated average weekly production to standing firm orders; the balance of his production should be sold on spot orders.

45. DISTRICT OF COLUMBIA GOVERNMENT. Policy order making impounded animals available for medical research. *Order* No. 58-1415, Sept. 4, 1958, Washington, D.C.

The new order including two previous ones, dated Feb. 23 and Nov. 19, 1954, transfers the functions of the D.C. Pound of the Metropolitan Police Dept. to the Dept. of Public Health. Regulations are published concerning allocation of impounded animals to approved institutions which then have to take care of the transportation costs. Standards concerning animal housing and feeding are listed. (*See also* Abstr. 6: 31)

46. DRUMMOND, R. O. Laboratory screening tests of animal systemic insecticides. *J. Econ. Entomol.* 51: 425-7 (Aug.), 1958.

Guinea pigs infested with nymphal lone star ticks and screwworms are treated orally or subcutaneously with the compounds to be tested. After treatment, stable flies are fed on the guinea pigs. Compounds showing promise in tests with guinea pigs were tested further in sheep and goats. (From author's summary)

47. GREAT BRITAIN, HOME OFFICE. Experiments on living animals. Return of experiments performed under the Cruelty to Animals Act, 1876, during 1957 (in continuation of *Parliamentary Paper* No. 287 of Session 1956–1957). London, H. M. Stationery Office, 1958, 6 pp.

An explanatory note on The Cruelty to Animals Act, 1876, relating to experiments with living animals, was published on July 31, 1958. The act imposes restrictions which apply to any experiment calculated to inflict pain upon a living vertebrate animal. The explanatory note discusses the different classes of licenses which are granted by the Secretary of State authorizing certain experiments. The 2nd part of the note contains a summary of experiments performed in 1957.

48. JONES, W. M., MARGOLIS, G. AND STEPHEN, C. R. Hepatotoxicity of inhalation anesthetic drugs. *Anesthesiology* 19: 715–23 (Nov.–Dec.), 1958.

The use of white mice of Swiss strain for evaluating the hepatotoxicity in inhalation of anesthetic drugs was demonstrated and a screening method for use in the laboratory was described. The following drugs were tested: chloroform, fluorothane, trichloroethylene, vinyl and ethyl ether. Histologic studies of the liver made 72 hr. after exposure showed chloroform and vinyl ether to be the most hepatotoxic drugs. Ethyl ether was relatively innocuous, and fluorothane, while producing fatty changes in the liver, failed to cause necrosis in the highest nonlethal dose employed.

XUM

49. MÜHLBOCK, O. Living animal material for biological research, Symposium in Gif-sur-Yvette, France. Oct. 6, 1958. *Information on Lab. Animals for Research, Natl. Research Council* 1, No. 10, Dec., 1958.

Since several tumors have never been encountered in mice, the possibility exists that mice are extremely resistant to these tumors. Therefore, other species must be investigated for the appearance of tumors. Author suggests that new inbred strains of rats be developed and made available for study.

50. U. S. FEDERAL TRADE COMMISSION. *Trade Practice Rules for the Rabbit Industry, as Promulgated June* 27, 1958. 8 pp.

These rules (a revision and extension, superseding those of 1934 for the Rabbit and Cavy Breeders' Industry) are directed to the prevention and elimination of various unfair trade practices as applying to all types, breeds, varieties, or strains of live domestic rabbits or cavies.

51. WEYDERT, K. A. A purchasing agent's view of animal colony procurement problems. *Proc. Animal Care Panel* 8: 37–40 (Mar.), 1958.

A purchasing policy manual is presented and discussed.

52. ANONYMOUS. It's a long journey from jungle to laboratory for monkeys. *Allied Veterinarian* 30: 76–9 (May–June), 1959.

Experience in the management of transportation by air of about 2,000 cynomolgus monkeys from the Philippine Islands to the Pittman-Moore Co. at Zionsville, Ind., is described. Mortality for the 24,000-mi. trip was about 1%.

53. CLARKSON, T. B. The white Carneau pigeon: A new tool for the study of atherosclerosis. *Information on Lab. Animals for Research, Natl. Research Council* 3: 5 (Oct.), 1959.

A strain of white Carneau pigeons from the Palmetto Pigeon Plant in Sumter, S. C., was found to develop spontaneously, on grain diets, atherosclerosis which grossly and microscopically was almost identical with the disease in man. The disease appears in the pigeons at about 7 mo. of age. No difference in total serum cholesterol, total lipid, phospholipid and β-lipoprotein were found between atherosclerosis-susceptible and resistant pigeons.

54. GAY, W. I. Tattooing of dogs used in medical research. *Proc. Animal Care Panel* 9: 75–77 (June), 1959.

The technique used at the National Institutes of Health for tattooing dogs is described. With appropriate modifications, the procedure is applicable to any species of large animals.

55. GLIMSTEDT, G. The germfree animal as a research tool. *Ann. N. Y. Acad. Sci.* 78, Art. 1: 281–4 (May), 1959.

The germfree animal may be a useful research tool in the following fields: problems bearing on the humoral and cellular defense mechanism of the body; possible relationships between bacteria and tumors; amebiasis; biochemistry and nutrition; monovalent infection; and others.

56. HARRIS, R. S. Isotopes in nutritional biochemistry. *Rev. Nutrition Research* 20: 39–59 (Aug.), 1959.

Experiments with isotopes in living animals are described.

57. LABORATORY ANIMAL BREEDERS ASSOCIATION. Report on meeting by E. SIMONSEN, Secretary. *Science* 130: 1714–15 (Dec. 18), 1959.

At the charter meeting of the Laboratory Animal Breeders Association in Chicago on Dec. 2, 1958, committees were established to consider regulatory activities, animal husbandry projects, relations of the association with other areas of the laboratory animal industry and a committee on shipping relations.

58. NATIONAL RESEARCH COUNCIL, INSTITUTE OF LABORATORY ANIMAL RESOURCES. *Animals for Research. A Catalogue of Commercial Sources.* 2nd ed., Washington, D.C., June, 1959, 45 pp.

The 1st edition of this catalogue appeared in April, 1958. Commercial sources of laboratory animals for medical and biological research workers, based on information furnished by the nation's commercial organizations, are listed.

59. NATIONAL RESEARCH COUNCIL, INSTITUTE OF LABORATORY ANIMAL RESOURCES, COMMITTEE ON ANIMAL CARE (N. R. BREWER, CHAIRMAN). *Dog Shipping Standards.* Mimeo, 2 pp., Dec. 7, 1959.

Dimensions of individual crates for dogs, from below 25 lb. to over 60 lb., should range from 16 x 24 x 18 in. to 24 x 46 x 36 in. If transported in pens, the minimum space assignments for dogs, below 25 lb. to over 45 lb., should range from 2 ft²/dog, 28 in. high, to 5 ft²/dog, 32 in. high. Food should be offered at least once every 24 hr., water every 12 hr. and at 90°F every 4 hours. The truck in which the dogs are shipped should be heated or ventilated, according to weather. Only compatible and healthy dogs should share the same pen.

60. ORLAND, F. J. A review of dental research using germfree animals. *Ann. N.Y. Acad. Sci.* 78, Art. 1: 285–88 (May), 1959.

Germfree animals are an important research tool for the study of oral microflora and the etiological aspects of oral disease in mammalian hosts.

61. SMYTH, H. F. The toxicological basis of threshold limit values: 1. Experience with threshold limit values based on animal data. *Am. Ind. Hyg. J.* 20: 341–5 (Oct.), 1959.

The use of experimental animals in inhalation studies, designed for establishing threshold limits, is discussed. (53 references)

62. TAYLOR, A. R. Theoretical and practical considerations of germfree animals in virology. *Ann. N. Y. Acad. Sci.* 78, Art. 1: 102–14 (May), 1959.

The germfree animal, in contrast to the conventional animal, provides a more standardized host for the study of infectious agents. The absence of microbial flora permits more uniform response to quantitated viral inocula. Studies on germfree animals are expected to contribute information in many areas of virology.

63. THORP, W. T. S. (Chairman). Animal experimentation: The care and use of laboratory animals. In: *National Conference on the Legal Environment of Medical Science*, sponsored by the National Society for Medical Research

and the University of Chicago, May 27–8, 1959, pp. 36–63.

The session, as summarized by THORP, included papers and reports under the following outline: terms, definitions and some historical background; legal recognition of animal experimentation; property rights in animals; anticruelty laws; private and public sources of animals; responsibilities of the commercial breeder and supplier; status of vivisection. The key paper was presented by J. F. SEMBOWER. A report of the Committee on the Mutual Responsibility of Suppliers and Research Workers Concerning Experimental Animals was presented by B. F. HILL, Chairman. B. J. COHEN, Chairman, presented a report of the Committee on the Legal and Ethical Factors Regarding Animal Experimentation. Guiding principles in the use of animals by secondary-school students and science club members, and of laboratory animal care as developed under the auspices of the National Society for Medical Research to supplant varying existing rules and regulations are included. The Oklahoma pound law is reprinted as an example of a complete, self-contained statute.

THE FOLLOWING ABSTRACTS, although located elsewhere in this bibliography, are related to the subject of this section.

Section 1: 87, 101, 106, 125, 135, 181, 208, 220, 229, 232, 245, 263 285, 314, 350, 371, 417, 418, 481, 498, 507, 510, 511.

Section 2: 9, 10, 30, 63 70, 80, 97, 101, 167, 192, 196, 215, 253, 256 262, 279, 318, 336, 352, 353, 367, 373, 375.

Section 3: 19, 40, 82.

Section 4: 2, 9, 10, 19, 21, 28, 35, 36, 37, 40, 44, 45, 53, 57, 58, 61, 65, 74, 76, 78, 90, 99, 100, 101, 105, 109, 112.

Section 5: 1, 12, 14, 27, 28, 30, 40, 49, 56, 61, 67, 87, 96, 97, 102, 109, 125, 128.

Section 7: 92, 94, 107, 115, 121, 143, 164.

Section 8: 1, 6, 16.

Section 9: 7, 9, 11, 12, 15, 17, 18, 19.

7. Special Techniques; Preparation of Animals for Use; Handling; Anesthesia; Euthanasia[1]

1. Huddleson, I. F. and Carlson, E. R.: A new animal board. *J. Lab. Clin. Med.* 13: 660–1 (Mar.), 1928.

An animal board, suitable for restraining rabbits, guinea pigs or rats, is described.

2. Hrdina, L. S. Electrocution in sacrificing laboratory animals. *J. Lab. Clin. Med.* 15: 86 (Oct.), 1929.

Electrocution of laboratory animals not larger than dogs, using 110-v. alternating current, is described.

3. Carmichael, E. B. A convenient preparation for the removal of hair. *Science* 75: 136–7 (Jan. 29), 1932.

An apparatus generating hydrogen sulfide and its use as depilatory is described. The method has been used for removing hair on dogs, rabbits, guinea pigs and white rabbits without any apparent deleterious effects.

4. Ivy, A. C. and Barry, F. S. Studies on the electrical stunning of dogs. *Am. J. Physiol.* 99: 298–307 (Jan.), 1932.

In order to produce a rapid anesthetic effect or stunning, dogs were subjected to various types of electrical current. The duration of the anesthesia, the effects of the current on various physiological mechanisms and the mechanism of the anesthesia were studied. A current of 72-v., interrupted 6000 times/min., was the most efficient, producing an anesthesia lasting an average of 2 min. 8 sec. By passing the current through water, it was convenient to make contact with the dog. Spinal analgesia was produced by placing 1 electrode on the back of the neck and the other over the lumbar region, using a current of 4–12 v. Daily application for 1 wk. caused no disturbance of the function of the spinal cord.

5. Seifried, O., Cain, C. B. and Wulf, H. A holder for chickens and other birds. *Science* 75: 315–16 (Mar. 18), 1932.

A board consisting of a sheet of metal supported on legs to form a low table was designed. It can be used for confining fowl quickly and firmly in either ventral, dorsal and lateral positions, without the aid of an assistant. The board is especially useful for bleeding chickens from the carotid and wing vein and for operations, photography and other laboratory procedures.

6. Bunster, E. and Meyer, R. K. An improved method of parabiosis. *Anat. Record* 57: 339–43 (Nov. 25), 1933.

A modification of Sauerbruck and Heyde's method of parabiosis, as performed on rats and mice, is described. The advantages of the method are presented.

7. Gaebler, O. H. Metabolism masks for dogs. *Proc. Soc. Exptl. Biol. Med.* 31: 500–2 (Jan.), 1934.

A durable mask is described which may be employed in energy metabolism experiments in which the same dog is used for 1 yr. or more.

8. Grant, R. T. and Rothschild, P. A device for estimating blood-pressure in the rabbit. *J. Physiol. (London)* 81: 265–9 (May), 1934.

The device, based on von Recklinghausen's method, is useful for estimating systolic blood pressure in the ear of normal and unanesthetized rabbits.

9. Apgar, C. S., Jr. A practical operating stand. *Science* 90: 22 (July 7), 1937.

An inexpensive operating stand for use in experimental surgery of laboratory animals is described.

10. Kniazuk, M. A method for determining the heart rate of small animals. *J. Lab. Clin. Med.* 22: 868–70 (May), 1937.

In the method described, the photokymograph and the electromagnetic oscillograph are replaced by a cathode ray oscillograph. For taking the EKG, the animal is placed in a special holder which must fit it snugly. Accurate measurements of the heart rate (±5 beats/min.) have been obtained in guinea pigs, rats, mice and other laboratory animals within 1–2 min. (No values are given.)

11. Syverton, J. T. and Berry, G. P. An improved instrument for the intracerebral inoculation of experimental animals. *Science* 86: 567–8 (Dec. 17), 1937.

The instrument used consists of a common nail filed to a point. A small incision is made through the skin of the anesthetized animal, the instrument is inserted through the skin and into the skull and the needle of the syringe is then injected along this groove. After the desired amount of inoculum is injected, needle and instrument are withdrawn together.

12. Whitaker, W. L. A method for studying environmental choices of laboratory animals. *Science* 86: 314 (Oct. 1), 1937.

An apparatus is described which records over a period of 10 days the time that a mouse spends in light or darkness by its own choice. The equipment is adaptable, for example, to record temperature choices of frogs, light choices of snails, or moisture choices of certain insects.

13. Burdon, K. L. A mouse holder facilitating intravenous inoculations. *J. Lab. Clin. Med.* 23: 1293–5 (Sept.), 1938.

The apparatus consists of a rectangular wooden box with a slot at the top and houses an electric light bulb. For intravenous injections the tail of the mouse is held over or within the illuminated slot so that the veins are clearly seen. The device may be used also for bleeding from these veins.

---

[1] Arrangement is chronological by year of publication. A list of additional references, located in other sections of this bibliography, will be found on page 132.

14. CHEN, K. K. AND ROSE, C. L. Small animal holders for intravenous injection. *J. Lab. Clin. Med.* 24: 750–2 (Apr.), 1939.

Holders for mice, rats and guinea pigs for intravenous injection or for securing blood samples are described. The holders are distinguished by simplicity of manipulation, complete immobilization of the animal and ease in cleaning.

15. GADDUM, J. H. A method of recording the respiration. *J. Physiol. (London)* 99: 257–64 (Jan. 14), 1941.

The principle of the method is that all the air breathed by the animal passes at an approximately steady rate through a resistance and a record is taken of the fall of pressure in this resistance. The method is illustrated in a conscious rabbit. It may be applied to conscious or anesthetized animals or to man.

16. JOHN, R. An improved electrically-heated operating board for small animals. *J. Physiol. (London)* 99: 157–60 (Jan.), 1941.

The apparatus described has been useful in performing aseptic operations on rats and mice. The special features of the device are a swiveling operating board which is electrically heated and the provision of adequate space for setting out instruments. An efficient anesthetic mask is also described.

17. KEELER, C. E. Simple floor-net for catching the escaped laboratory rodent. *Science* 93: 408 (Apr. 25), 1941.

A net, as described and illustrated, is laid on the floor, the animal is driven into the bag and the opening is then closed. The equipment may be used for common laboratory rodents, such as the rat, mouse, guinea pig, or in a larger size for rabbits and in a smaller size for wild rats.

18. DONNELLY, G. L. Permanent devocalization of dogs by removal of both the true and the false vocal cords. *Proc. Soc. Exptl. Biol. Med.* 50: 79–80 (May), 1942.

A method for removing both the true and false vocal cords of dogs is described. Animals still living 8–9 yr. after the operation have had no return of vocal powers. However, if only the true vocal cords are removed, the dogs learn to bark a.gain

19. FLEISCH, A. AND POSTERNAK, J. Die posttraumatische Verkürzung der Blutungszeit. (The posttraumatic shortening of the bleeding time.) *Helv. Physiol. et Pharmacol. Acta* 1, No. 2: 199–204, 1943.

A method for the determination of the bleeding time in the rabbit after incision of the ears is described. Several factors which may be responsible for the phenomenon of posttraumatic shortening of the bleeding time were investigated.

20. GOETZL, F. R., BURRILL, D. Y. AND IVY, A. C. A critical analysis of algesimetric methods with suggestions for a useful procedure. *Quart. Bull. Northwestern Univ. Med. School* 17: 280–91, 1943.

The theoretical requirements for an ideal method of algesimetry are discussed with reference to the type of stimulus (mechanical, thermal, chemical or electrical), receptive field (skin, cornea, mucous membrane, intestinal wall or tooth pulp) and nature of response. A method of algesimetry is suggested and an apparatus is described which provided induced, uninterrupted, low voltage, alternating current in peaks of voltage variable at will and of short and measurable duration. In experiments with dogs the first distinctly perceptible twitch of an isolated muscle or muscle group was regarded as the standard response. The "thresholds" on 2 cuspid teeth were determined for every dog as measured in volts.

21. LAUG, E. P. A multiple rabbit holder. *J. Lab. Clin. Med.* 29: 308–11 (Mar.), 1944.

The holder described immobilizes the animal in a manner similar to a head and hip stock but without restricting movement of fore or hind limbs. It is useful when immobilization of rabbits for extended periods is desired. The holder could be modified to accommodate dogs and cats.

22. DETERLING, R. A., JR. AND ESSEX, H. E. A tail plethysmograph for measuring arterial blood pressure in dogs. *Proc. Soc. Exptl. Biol. Med.* 58: 247–9 (Mar.), 1945.

The tail plethysmograph as used on the rat has been modified for use on the dog. When properly applied, it affords an easy and repeatable measure of arterial blood pressure in close agreement with values obtained by the mercury manometer. (Author's summary)

23. DEICHMANN, W. B., KITZMILLER, K. V., DIERKER, M. AND WITHERUP, S. Observations on the effects of diphenyl, *o*- and *p*-aminodiphenyl, *o*- and *p*-nitrodiphenyl and dihydroxyoctachlorodiphenyl upon experimental animals. *J. Ind. Hyg. Toxicol.* 29: 1–13 (Jan.), 1947.

A new stock for immobilizing a rabbit in the supine position is described and illustrated.

24. BOLLMAN, J. L. (With the assistance of VAN HOOK, E.) A cage which limits the activity of rats. *J. Clin. Lab. Med.* 33: 1348 (Oct.), 1948.

A cage was developed to restrain a rat during periods of days while an indwelling tube is in place for collection of urine, for continuous or intermittent injection through a tube inserted into a vein, for collection of lymph from the thoracic duct, intestine, or liver, etc. A photograph accompanies the brief description.

25. BOLLMAN, J. L., CAIN, J. C. AND GRINDLEY, J. H. (With the Technical Assistance of VAN HOOK, E.) Techniques for the collection of lymph from the liver, small intestine, or thoracic duct of the rat. *J. Lab. Clin. Med.* 33: 1349-52 (Oct.), 1948.

The technique described is useful in the study of lymph from the standpoint of the substances exchanged from the plasma to the lymph and of the materials contributed to the lymph from the intestine in the course of digestion and absorption of various foods.

26. MARSH, D. F. A convenient apparatus for recording the blood pressure of small animals. *Science* 108: 393 (Oct. 8), 1948.

A simple apparatus, using the Lambert-Wood strain-gauge manometer, is described. If only the mean blood pressure is measured, this device provides an improvement over existing methods.

27. PITESKY, I. AND LAST, J. H. An effective depilatory formula for use on laboratory animals. *Science* 108: 657 (Dec. 10), 1948.

A depilatory is prepared by triturating ⅔ by weight of purified yellow Ba sulfide powder with ⅓ by weight of a commercial detergent. Application of the depilatory is described. It has been used for rabbits, mice, dogs, cats, and monkeys without giving any indication of secondary infections or delayed wound healing.

28. Princi, F., Church, F. and McGilvray, W. An improved animal dusting apparatus. *J. Ind. Hyg. Toxicol.* 31: 106–12 (Mar.), 1949.

An animal exposure chamber was constructed from soap drums in which only the animal's head gets into contact with the material to be inhaled. The apparatus is useful for determining the toxic effects of materials in conditions that approximate those encountered in industry. Dogs have been exposed for over 6 mo. with good results.

29. Feist, J. H. and Petrie, S. J. A holding-board for small laboratory animals. *Am. J. Clin. Pathol.* 20: 691–2 (July), 1950.

A wooden holding-board with rubber strips which prevents the animal from struggling with its hind paws was designed. It was found to be satisfactory for studies which require intravenous injections of unanesthetized animals.

30. Ambrus, J. L., Ambrus, C. M., Harrisson, J. W. E., Leonard, C. A., Moser, C. E. and Cravetz, H. Comparison of methods for obtaining blood from mice. *Am. J. Pharm.* 123: 100–4 (Mar.), 1951.

Swiss male mice were used for a study of different methods of taking blood. Methods are described for obtaining *1*) mixed venous and arterial blood, *2*) pure venous or pure arterial blood, *3*) small amounts for blood counts and *4*) blood from embryos or newborn mice. A line drawing of the collecting tube is given.

31. Hansard, S. L. Radioisotope procedures with farm animals. I. Metabolism facilities. II. Quantitative administration and blood-sampling. *Nucleonics* 9: 13–25 (July), 38–45 (Aug.), 1951.

Functional metabolism units are described for radioisotope balance studies with swine, sheep and cattle. Methods for taking blood samples and administering isotopes are discussed.

32. Harrisson, J. W. E., Ambrus, J. L. and Ambrus, C. M. A simple aerosolizing apparatus for the production of experimental asthma. *J. Am. Pharm. Assoc., Sci. Ed.* 40: 226–8 (May), 1951.

An aerosol apparatus, easy to construct and applicable to the determination of the sensitivity of guinea pigs toward histamine, acetylcholine, or antigens, is described. The method described is useful to test antihistaminic, parasympatholytic, antianaphylactic, or antispasmodic drugs.

33. Leahy, J. R. and Barrow, P. *Restraint of Animals.* Ithaca, N. Y., Dept. of Anatomy, New York State Veterinary College, Cornell University, 1951, 235 pp.

Basic rope work restraint techniques are described and illustrated in an early chapter. The remaining chapters present clearly, with ample illustration, techniques for catching, holding, carrying, restraining animals. The following are included: horse, cow, pig, dog, cat, fox, mink, rabbit, chicken and other fowl.

34. Vallejo-Freire, A. A simple technique for repeated collection of blood samples from guinea pigs. *Science* 114: 524–5 (Nov. 16), 1951.

The procedure described allows the withdrawal of small amounts of blood up to 14 times from the same guinea pig in 1 day. It is believed that the method may be used also on rats. The bleedings were obtained from nail insertions at the base of the toe nail after previous irradiation of the foot by an infrared ray lamp for 10 sec. Well-fed healthy animals may be bled without irradiation. Blood is collected with a capillary pipette from a slide or directly from the cut.

35. Woke, P. A. A rabbit-ear cage for bloodsucking arthropods. *U.S. Public Health Repts.* 66: 464–71 (Apr. 13), 1951.

A cage was designed specifically for attachment to the heads of rabbits in such a manner as to make full use of the enclosed ears in providing for the feeding of bloodsucking arthropods. The device may be adaptable to other animals.

36. Bester, J. F. A study of the potentiation of pentobarbital anesthesia by glucose and its metabolites. Dissertation, Ohio State Univ. 1952, 119 pp.

Glucose prolongs the sleeping time induced by pentobarbital in rats. Upon recovery from pentobarbital anesthesia rats are returned to sleep by the injection of concentrated solutions of glucose. (From *Dissertation Abstr.* 17: 2633–6 (Nov.), 1957)

37. Detrick, L. E. and Rhodes, B. A note on an apparatus for prolonged and repeated intravenous infusions in large animals. *J. Am. Pharm. Assoc. Sci. Ed.* 41: 283 (May), 1952.

A modification of the catheter used for prolonged and repeated infusions into the external jugular vein is described. No occlusions formed within the tubing in 16 rabbits, catheterized with this assembly, following 11 daily injections or 11 injections plus a 14-day recovery period.

38. Johansen, E. A new technique for oral examination of rodents. *J. Dental Research* 31: 361–5 (June), 1952.

A device for immobilization of the animal is described. A dissection microscope is then employed for the examination and magnification of the molars. The method is simple, quick and noninjurious to the animal.

39. Joslin, D. A tissue chamber and splint for the mouse. *Science* 115: 601–3 (May 30), 1952.

A splint and chamber for studies of skin grafts was constructed from Cu wire, sheet Lucite and solder. The device is tolerated for 4 wk. or longer, provides adequate immobilization, protection and proper circulation. Splint and chamber are placed over the circular wound or graft; a seal of fibrin from the exudate will cement the outer edge of the chamber to the edge of the circular wound. The mouse tissue chamber is illustrated.

40. Albert, S., Johnson, R. M. and Wagshal, R. R. Effect of nuclear counting procedures on determination of the desoxypentosenucleic acid content of rat liver cell nuclei. *Science* 117: 551–3 (May 22), 1953.

Author points out that the use of glass pipettes as part of the procedure for counting rat liver cell nuclei in final nuclear preparations employing a medium of either citric acid or sucrose is contraindicated while the use of a wire loop circumvents the counting difficulties encountered with pipettes.

41. Archibald, R. T., Fraser, R. and Chapman, C. B. A collecting device for obtaining blood samples at

various intervals from an intra-arterial catheter. *Science* 118: 390–1 (Oct. 2), 1953.

The device employs polyethylene catheters for insertion into arteries for repeated or continuous sampling. It consists of 5 main components: *1*) a wooden base through which protrudes the open end of a brass tube connected on the outside to an evacuation pump; *2*) plastic spools to carry 21 tubes for collecting blood; *3*) a ratchet system for moving the spool; *4*) a modified antenna relay and solenoid to provide thrust and retraction to an actuating arm operating the ratchet; and *5*) a glass battery jar fitted tightly to the wooden base and provided with a 10-mm opening, placed directly over the circumference described by the collecting tubes, and fitted with a rubber stopper. The device can be used, with or without the vacuum, for the collection of other biological specimens at various time intervals. The application described is on a human subject.

42. ARMIN, J. AND GRANT, R. T. The artery of the denervated rabbit's ear as a sensitive pharmacological test object. *J. Physiol. (London)* 121: 593–602 (June), 1953.

A method is described for the intra-arterial injection of solutions into the central artery (ear) or the living anesthetized rabbit, and for obtaining reproducible responses to successive equal doses. It is useful for studying the reactions of the peripheral vessels and for detecting vasoactive substances in high dilution and in small volume. The apparatus used is described and illustrated. The method is applicable to tissue extracts and to rabbit's blood. (Author's summary modified)

43. BAURMASH, L., BRYAN, F. A., DICKINSON, R. W. AND BURKE, W. C., JR. A new exposure chamber for inhalation studies. *Am. Ind. Hyg. Assoc. Quart.* 14: 26–30 (Mar.), 1953.

An inhalation chamber using a rotating platform in a circular chamber has been developed for use in the study of the effect of airborne contaminants. The chamber is designed for ease of animal handling, chamber cleaning and decontamination and avoids "dead" spots. The chamber lends itself also to the use of radioactive materials in inhalation studies.

44. BISHOP, E. J. A method of visualizing the urinary tract and a basis for assessing renal function in small animal radiography. *J. Am. Vet. Med. Assoc.* 123: 187–92 (Sept.), 1953.

Retrograde and intravenous pyelography are discussed and 56 pairs of kidneys from dogs and cats were examined by i.v.p. Unsatisfactory radiographs were obtained when the contrast medium was employed in a 35% wt/vol. concentration while a 70% wt/vol. concentration produced consistent diagnostic results in normal animals. The need for thorough preparation and anesthesia of the animals and for adequate x-ray films is emphasized. A dosage scale of contrast medium in radiography of small animals is given. Two dogs and 4 cats were examined by injecting the dye into the biceps femoris.

45. BOURA, A. AND DICKER, S. E. An apparatus for the maintenance of a constant water load and the recording of urine flow in rats. *J. Physiol. (London)* 122: 144–8 (July), 1953.

An apparatus for recording the urine flow of rats while maintaining a constant water load is described and diagrammed.

46. BRUNST, V. V. AND CLAYTON, R. J. Photographing small laboratory animals. *Lab. Invest.* 2: 376–87 (Sept.-Oct.), 1953.

The photographing of small animals such as mice or salamanders presents special problems concerning proper background and lighting, particularly when the animals are photographed in water or without anesthetics. Suitable devices as well as the standard type of focusing for taking photographs to scale is described.

47. COLERIDGE, J. C. G. AND LINDEN, R. J. Recording of effective right and left atrial pressures in the intact dog. *J. Physiol. (London)* 122: 65–7P (Sept.), 1953.

Effective pressures in the right and left atria can be measured in the anesthetized dog with the chest unopened. Effective atrial pressure is equal to atrial pressure minus intrathoracic pressure; the latter was measured in 2 ways. A sample analysis of 2 cardiac cycles is given.

48. DELAY, J. AND THUILLIER, J. E. Curarization by rectal suppository. *Science* 117: 57 (Jan. 16), 1953.

The advantages of rectal administration of curare to rabbits compared to i.v. injection are discussed. Rectal administration results in slower curarization, more persistent effect and slower recuperation of muscular contractility.

49. DEWS, P. B. The measurement of the influence of drugs on voluntary activity in mice. *Brit. J. Pharmacol.* 8: 46–8 (Mar.), 1953.

A method is described which distinguishes qualitatively between co-ordinated running or walking movements and twitching or convulsive movements in mice. The influence of such drugs as epinephrine, methamphetamine, strychnine, nicotine, picrotoxin, cocaine, amphetamine, ephedrine, caffeine, on co-ordinated activity in male albino mice of Carworth Farms CF-1 strain was studied.

50. FERGUSON, I. D. AND GRAY, A. T. Acute decerebration in the greyhound. *J. Physiol. (London)* 122: 69P (Sept.), 1953.

Arterial ligation was carried out bilaterally in the neck of the anesthetized dog and the brain stem was transected in the midline. The technique was successful only in about 50% cases, with survival times of about 24 hr.

51. GOLDWASSER, R. AND SHELESNYAK, M. C. A syringe carrier and egg clamp for intravenous inoculation of chick embryo. *Science* 118: 47–8 (July 10), 1953.

In order to overcome the prohibitively high casualty rate resulting from "free hand" injection and bleedings, an apparatus was designed which consists of a rigid movable syringe carrier and an adjustable egg clamp. The device permits the accurate and precise placement of the hypodermic needle at the proper angle, and entry into and removal from the blood vessel, without erratic motion.

52. GOODALE, W. T. AND HACKEL, D. B. Measurement of coronary blood flow in dogs and man from rate of myocardial nitrous oxide desaturation. *Circulation Research* 1: 502–8 (Nov.), 1953.

A technique of measuring left ventricular coronary blood flow in dogs and man from the rate of myocardial nitrous oxide desaturation has been presented. The desaturation technique is considered valid in comparison with the saturation technique and affords definite technical advantages.

53. GRAY, R. S. AND AXELROD, A. E. Application of thermistor to measurement of subcutaneous tempera-

tures during hydrothermal injury in the rat. *Proc. Soc. Exptl. Biol. Med.* 83: 269–72 (June), 1953.

A simple and sensitive thermoelectric device for the measurement of temperature is described which incorporates the thermistor as the temperature-sensing element. As a needle-type thermometer, this apparatus has been used extensively to obtain continuous recordings of abdominal subcutaneous temperatures attained during the production of hydrothermal burns in rats. (Condensed from author's summary)

54. Haley, T. J. and Dickinson, R. W. A simple apparatus for observation of mesenteric capillary blood flow in rats. *Arch. intern. pharmacodynamie* 95: 243–5 (Sept.), 1953.

A modification of Zweifach's apparatus for microscopic observation of blood flow in the mesoappendix of the rat is described. Better control of the temperature of the fluid is achieved by using the warming bath of the Anderson-Craver heart perfusion apparatus for warming the perfusion fluid.

55. Hansard, S. L. and Comar, C. L. Radioisotope procedures with laboratory animals. *Nucleonics* 11: 44–7 (July), 1953.

General management, isotope administration and balance studies after administration to mice, rats or guinea pigs are described.

56. Hyman, C., Stone, A. and Sosnow, M. Application of tissue clearance technics in small animals. *Proc. Soc. Exptl. Biol. Med.* 83: 643–6 (July), 1953.

In short-term investigations (5–10 min.) the clearance of radioisotopes from various sites of injection in rats, rabbits and dogs was quite linear. If, however, the period of observation was extended beyond 30 min., deviations from this simple relationship were found. Experiments with pentobarbital anesthetized rabbits showed that a major factor responsible for the nonlinear tissue clearances was the return of the isotope to the area of injection in the arterial blood. Exponential clearances could be obtained by subtracting the simultaneously measured activity over a corresponding area of tissue from the count over the injection site.

57. Kassel, R. and Levitan, S. A jugular technique for the repeated bleeding of small animals. *Science* 118: 563–4 (Nov. 6), 1953.

Using the described technique of venipuncture, it has been possible to obtain blood samples from weanling mice, and older animals have been bled a total of 12 times within 6 wk.

58. Linder, M. J. Estimation of growth rate in animals by marking experiments. *U.S. Fish Wildlife Serv., Fishery Bull.* No. 78: 65–9, 1953.

A measurement technique for estimating growth and age in laboratory animals is described.

59. Littlewood, G. and Platts, T. L. A simple apparatus for repeated intratracheal injections in rats. *J. Animal Technicians Assoc.* 4: 53 (Dec.), 1953.

A line drawing illustrates the apparatus, constructed of a plastic (Perspex) in such a manner as to secure the rat's head and immobilize its forelegs. Intratracheal injection was accomplished by passing a needle through the larynx under anesthesia, without resorting to surgery.

60. Norris, W. P. and Flynn, R. J. Considerations in the use of radioactive isotopes in animal experimentation. *Proc. Animal Care Panel*, 4th Ann. Meeting, Chicago, Dec. 2–3, 1953, pp. 106–14.

Protective measures in work with radioactive isotopes and disposal of contaminated waste is discussed.

61. Ryckman, R. E., Fischer, K. C., Ames, C. T. and Lindt, C. C. The electric fence as an aid in field studies of rodents and their ectoparasites. *Calif. Fish and Game* 39: 489–96 (Oct.), 1953.

A method of constructing a mechanical and electrical fence has been perfected to retain or exclude the California ground squirrel *Citellus beecheyi beecheyi* (Richardson) and *C. beecheyi fisheri* (Merriam). Rats of the genus *Rattus* have also been confined to a pen 15 ft.^{2} by the use of a specially designed electric fence for studies to determine if such a fence can be used to protect stored products susceptible to rat damage. Illustrations are given of the fences and of a live trap, which was the most successful for capturing the California ground squirrel. (Condensed from author's summary)

62. Selye, H. Use of "granuloma pouch" technic in the study of antiphlogistic corticoids. *Proc. Soc. Exptl. Biol. Med.* 82: 328–33 (Feb.), 1953.

The "granuloma pouch" technique has been devised as a procedure for the quantitative analysis of factors regulating inflammation and wound healing. Experiments with rats showed that striking changes occur in the granuloma pouch upon topical administration of hydrocortisone acetate.

63. Algire, G. H. Determination of peripheral blood pressure in unanesthetized mice during microscopic observation of blood vessels. *J. Natl. Cancer Inst.* 14: 865–76 (Feb.), 1954.

A method utilizing a membrane manometer system is described for indirect measurement of peripheral blood pressure in vessels within transparent chambers in mice. The measurements obtained are considered as relative rather than absolute. (Condensed from author's summary)

64. Barnes, J. M. and Denz, F. A. Experimental methods used in determining chronic toxicity. A critical review. *Pharmacol. Revs.* 6: 191–242 (June), 1954.

An extensive review with 320 references. The following aspects are covered: design and execution of chronic toxicity tests with animals (choice and numbers, species variation in susceptibility to toxic substances, genetic factors, choice of sex); administration of compounds (purity, doses, oral route, inhalation, other routes); feeding; results of toxicity tests and their interpretation, assessment of human hazards.

65. Berkeley, W. H. An instrument to simplify bone drilling and injection. *Science* 120: 398 (Sept. 3), 1954.

A bone drilling and injection device for making intracerebral injections in monkeys was described and illustrated. It can be adapted for use with any species of animal.

66. Best, C., Bolam, R. and Hallpike, C. S. A new head-holder for rabbits. *J. Physiol. (London)* 123: 22–3P (Dec. 1953), 1954.

A head-holder for rabbits, which can be readily applied, causes no injury, and provides an extreme degree of immobility, is described.

67. DENIZ, N. AND GREGERSEN, M. I. Bleeding volume in dogs. *Federation Proc.* 13: Abstr. No. 114 (Mar.), 1954.

A simple apparatus consisting of a polyethylene container suspended by a calibrated spring was used for recording the bleeding volume on a kymograph. With this arrangement dogs were bled several times (6–10) in succession to study the effects of various experimental conditions on the bleeding volume.

68. EAYRS, J. T. An apparatus for analyzing the pattern of spontaneous activity in laboratory animals. *Brit. J. Animal Behaviour* 2: 20–4, 1954.

An apparatus is described which has been designed to analyze the spontaneous activity of small laboratory animals into the following components: the distance run, hour by hour; the proportion of each hour spent in running; and the velocity of running. The apparatus can readily be modified to analyze activity into shorter or longer intervals than 1 hr. (Author's summary)

69. HACKL, H. Eine einfache Vorrichtung zur Narkotisierung von Versuchstieren. (A simple procedure for narcotizing laboratory animals.) *Arch. Hyg. u. Bakteriol.* 138: 436–9 (Oct.), 1954.

A simple, homemade device (consisting of a glass container with attached glass tube and hose) is described for narcotizing laboratory animals, without the help of an assistant. In 78 laparotomies, nephrectomies, etc., 1 rat and 1 guinea pig were the only fatalities.

70. HADGRAFT, J. W. AND SOMERS, G. F. A method for studying percutaneous absorption in the rat. *J. Pharm. and Pharmacol.* 6: 944–8 (Dec.), 1954.

The rat when injected with acetylcholine secretes opaque reddish brown tears. This sensitivity to acetylcholine is increased considerably by such anticholinesterase drugs as Eserine. The magnitude of the response was used to study the percutaneous absorption of Eserine and its salts from various ointment bases.

71. SINGER, M. Apparatus for continuous infusion of microvolumes of solution into organs and tissues. *Proc. Soc. Exptl. Biol. Med.* 86: 378–80 (June), 1954.

An apparatus is described for infusion of small volumes of test solutions directly into tissues and organs. In more than 3000 successful infusions of the early regenerating limb of salamanders, volumes of 0.001 cc/hr. have been introduced for periods of 5 or more hr. The apparatus consists of an advancing bar which is driven forward by a screw shaft attached to a clock motor. The advancing bar presses against the plungers of small syringes forcing fluid into fine polyethylene tubing and thence through a glass capillary needle into the tissues.

72. BIÖRCK, G., DAMGAARD-NIELSEN, M., HAEGER, K., RYD, H. AND WULFF, H. B. Box for refrigeration and rewarming in animal experimentation and human surgery. *Scand. J. Clin. and Lab. Invest.* 6: 277–83, 1955.

A refrigerator unit, also fitted with heating radiators for rewarming, is presented. Experiments with dogs, cooled to a body temperature of about +20°C at a box temperature of as low as −6°C, are reported.

73. BORÉUS, L.-O. AND SANDBERG, F. A comparative study of different algesimetric methods in animals and man. *Acta Pharmacol. Toxicol.* 11: 198–214 (Aug.), 1955.

Pain response and effects of analgesics were studied by electrical stimulation of the tooth pulp in dogs, cats and man, and radiant heat stimulation of the skin in rats and man. A diagram shows the scheme for the stimulation of tooth pulp in the dog; typical threshold response of dogs and cats is described and illustrated in the case of the dog.

74. BRYANT, B. F. AND BERNARD, V. M. A new method for bandaging mice receiving free skin grafts. *Transplantation Bull.* 2: 133–4 (July), 1955.

Application of the bandage and sources of supply are given.

75. CASTANERA, T. J., KIMELDORF, D. J. AND JONES, D. C. An apparatus for measurement of activity in small animals. *J. Lab. Clin. Med.* 45: 825–32 (May), 1955.

The mechanical apparatus for the measurement of diffuse activity of small animals consists of a spring-suspended, stabilized cage and an integrator, made of modified clock parts, which yields a cumulative, numerical index of the animal's activity. An automatic watering system for use with the unit is described and an instrument for calibrating the unit has been devised. Although the apparatus has been used with rats and guinea pigs, slight adjustments of the existing parts should make the unit adaptable for use with other small animals.

76. COHEN, C. A method for bleeding rabbits. *Am. J. Clin. Pathol.* 25: 604 (May), 1955.

To obtain relatively large amounts of blood, a commercially available vacutainer device (Vacutainer Specimen Tube: Becton, Dickinson & Co.) is used. The procedure is as follows: The tube is evacuated either by a filter pump or by a syringe. The area of the central artery of the rabbit's ear is massaged. When the artery is sufficiently enlarged, a 23-, 24-, or 25-gauge needle fastened to the adapter is forced into the vessel. When blood begins to drip through the other end of the adapter the evacuated tube is pushed into place, so that the rubber stopper is pierced by the needle end of the adapter. The blood then flows at a steady rate into the tube. A 2nd evacuated tube can be filled simply by pulling the 1st tube out of the holder and inserting a 2nd tube. In this manner, as many as 3 tubes, each containing more than 15 ml have been filled. Precaution: the vacutainer holders are made of a plastic which is easily etched by xylene.

77. CROFT, P. G. Euthanasia. *Vet. Rev. and Annotations* 1, Pt. 1: 42–54, 1955.

Methods for euthanasia and their interrelationship with the purpose for which the animal is to be killed are explained. Management before slaughter, humane methods of slaughter, humane killers, electric stunning, bleeding, ritual slaughter, severance of spinal cord, CO_2 anesthesia, electrocution and killing by drugs are discussed.

78. FUSON, R. B. AND EICHWALD, E. J. A semi-automatic needle for implanting tissues into experimental animals. *Cancer Research* 15: 162–3 (Mar.), 1955.

A device for the rapid implantation of solid tissue fragments under aseptic conditions is described. One individual can operate the instrument and do 60 implants an hour. The percentage of successful implants is equivalent to that obtained by loading a separate cannula for each injection. (Author's summary)

79. GHOSH, M. N., AND SCHILD, H. O. A method for the continuous recording of acid gastric secretion in the rat. *J. Physiol.* (*London*) 128: 35–6P (Mar.), 1955.

XUM

The stomach of the anesthetized rat is perfused with a solution of NaOH and changes of pH following the i.v. injection of drugs are recorded continuously. The method can be used for the assay of stimulants and inhibitors of gastric secretion.

80. KNIAZUK, M. AND PREDIGER, R. F. Sonic gas analyzer for measuring respiratory gases. *Merck Institute for Therapeutic Research, Paper* No. 55-9-2, 1955, 5 pp.

Instruments such as the Pauling meter for O_2, the Lilly N_2 meter and the Fowler infrared analyzer, which employ different physical principles, are available for the analysis of specific gases. These instruments are highly sensitive and give practically instantaneous responses. The sonic gas analyzer described, while nonspecific for the individual gases, has the advantage of being highly sensitive, stable in operation, simple to manipulate and economical in technician time. Although the sonic gas analyzer was devised primarily for the study of respiratory gases, its flexibility and sensitivity suggest many other possible applications among which are: monitoring of gas mixtures that are made up on a continuous flow basis, since inherently the response is practically instantaneous and the sensitivity is the same over the range of 0 to 100%; analyzing mixtures of inert gases; testing the effectiveness of various gas absorbers at different flow rates; determining whether a gas sample is homogeneous; and following relative changes in the concentration of isotopes in certain gases. The device was used for a series of metabolism tests on 24 growing rats. (From author's discussion)

81. SIMMONS, J. S. AND GENTZKOW, C. J. *Medical and Public Health Laboratory Methods.* 6th ed. Philadelphia, Lea, 1955, 1191 pp.

Part 1 on clinical pathology includes urine, renal and liver function tests, hormonal tests for pregnancy, gastric and duodenal fluids, feces, sputum, transudates and exudates, cerebrospinal fluid, blood, blood group determination, blood transfusion, serodiagnosis of syphilis. Part 2 deals with chemistry (H ion, urinalysis, blood, food, toxicology). Parts 3–8 are concerned with mycology, bacteriology, rickettsiae and viruses, protozoology, helminthology and entomology. In part 9 pathology is discussed, in part 10, special veterinary laboratory methods, and in part 11, statistical methods.

82. BEINFIELD, W. H. AND LEHR, D. Advantages of ventral position in recording electrocardiogram of the rat. *J. Appl. Physiol.* 9: 153–6, (Sept.), 1956.

The electrocardiogram of the nembutalized rat was recorded with the animal in "unrestrained" prone position. The animal's legs were made to protrude through appropriate cutouts of a Lucite platform into four saline-filled beakers which served as electrode contacts. It is concluded that the ventral position in recording the electrocardiogram of the rat appears to possess definite advantages over the routinely employed dorsal position. (Condensed from author's abstract)

83. COLUMBUS, A. AND ZAUSCH, M. Eine Anlage für langdauernde Respirationsversuche an mittelgrossen Tieren (Schweine, Schafe, Ziegen). (Unit for long-continued respiration studies with medium-sized animals (hogs, sheep, goats).) *Arch. Tierernähr.* 6: 257–78, 1956.

The apparatus consists of the following parts: *1*) preexperimental metabolism boxes, *2*) respiration units with a special ventilation system, *3*) gas meters for measuring the volume of the experimental air, *4*) installations for testing and analyzing the fresh and experimental air, *5*) an air-conditioning system to produce experimental air of constant temperature and humidity, and *6*) a pump for moving the air in the desired quantity.

84. DRAPER, H. H. AND ROBBINS, A. F. A urinofecal separator for laboratory rat. *Proc. Soc. Exptl. Biol. Med.* 91: 174–5 (Jan.), 1956.

A glass separator of new design was developed which effects separation of urine and feces with a high order of efficiency. Design and operation of this apparatus are described.

85. DYCE, K. M. Veterinary radiology (myelography). *X-Ray Focus* 1, No. 3, pp. 6–7, 1956.

Myelography in dogs can assist the diagnosis of pressure on the spinal cord by a protruding intervertebral disc. Contrast medium is usually injected at the atlanto-occipital articulation. The type of needle employed is important. Of the 3 media which the author has used "myodil" appears to be the most suitable; iodized oil does not mix with the cerebrospinal fluid and "Thorotrast" is both irritant and radioactive. (*Vet. Bull.* 27: Abstr. No. 1537, 1957.)

86. GRAY, D. E. AND DELUCA, H. A. Use of desoxyribonucleic acid as a reference standard in metabolic experiments. *Am. J. Physiol.* 184: 301–3 (Feb.), 1956.

Data are reported on the metabolic activity of diaphragms from Sprague-Dawley rats fed a basal and low-protein diet, respectively. The indices of metabolic activity are expressed on a per cell basis, calculated on the content of desoxyribonucleic acid phosphorus.

87. GUYTON, A. C. AND GREGANTI, F. P. A phsyiologic reference point for measuring circulatory pressures in the dog—particularly venous pressure. *Am. J. Physiol.* 185: 137–41 (Apr.), 1956.

A physiologic reference point for measuring pressures in the circulatory system has been located by rotating dogs into all positions in space and locating the axes of rotation at which least variation in right atrial pressure occurs. This point remains extremely precise from one animal to another and also extremely precise regardless of the state of the circulation of the animal. It was found to be located approximately in the lower portion of the right ventricle described by the following dimensions: *a*) midway between the 2 lateral margins of the chest; *b*) anterior to the back 0.614 times the thickness of the chest; *c*) caudal to the sternal notch 0.767 times the distance from the sternal notch to the tip of the xiphoid process. (From author's summary)

88. HORVATH, M., MIKISKAU, A. AND PAŘÍZEK, O. Methodik des chronischen elektronencephalographischen Versuches am Kaninchen (für toxikologische und andere Zwecke). (Technique of the chronic electroencephalographic experiment in the rabbit (for toxicologic and other purposes).) *Pracovní lékařství* 8: 426, 1956.

The following manipulations are described: preparation of permanent epidural subcortical electrodes for leading electrical potentials from the brain to the electrical stimulus; surgical procedure; the application of a nasal electrode; an EEG equipment which makes it possible to take the EEG under all experimental conditions; a simple stroboscope; and the recording of the pneumogram. (*Zentr. Arbeitsmed. u. Arbeitsschutz* 9: 151 (June), 1959)

89. IRWIN, S., STAGG, R. D., DUNBAR, E. AND GOVIER, W. M. Methitural, a new intravenous anesthetic: Comparison with thiopental in the cat, dog and monkey. *J. Pharmacol. Exptl. Therap.* 116: 317–25 (Mar.), 1956.

The freshly prepared anesthetics were administered i.v. to the cat, dog and monkey (*Macaca mulatta*) over an interval of 3–5 min.

The characteristics of induction, anesthesia, recovery, untoward side effects, muscle relaxation, and cardiac and respiratory changes were observed. Methitural possessed about ⅔ the anesthetic potency of thiopental. Recovery following methitural was more rapid; repeated doses produced less cumulative action, less respiratory depression and less cardiac acceleration. Microscopic examination of the tissues after chronic administration showed thiopental to be considerably more toxic to the liver than methitural.

90. SUNDERMAN, F. W., KINCAID, J. F., KOOCH, W. AND BIRMELIN, E. A. A constant flow chamber for exposure of experimental animals to gases and volatile liquids. *Am. J. Clin. Pathol.* 26: 1211–18 (Oct.), 1958.

An animal exposure chamber was designed for inhalation studies of toxic gases and vapors. This chamber provides constant flow of gas, controllable over a wide range of flow-rates. The construction permits the use of a variety of experimental animals that may range in size from mice to 25-kg dogs. A special feature of the chamber is the insertion of baffles in order to provide uniform distribution of the toxic agent. The construction and operation of the chamber are outlined in the text. Detailed specifications are given in the appendix. (From author's summary)

91. ADELMAN, W. J., JR. AND CRISCUOLO, D. The Sarnoff phrenic stimulation technic for producing experimental hyperventilation in animals. *U. S. Air Force, School of Aviation Medicine Rept.* 57–68, Feb., 1957, 4 pp.

Electrophrenic hyperventilation of lightly anesthetized cats was achieved using a standard unmodified laboratory stimulator. (Condensed from author's summary)

92. ANONYMOUS. Medical research and animal welfare. *Brit. Med. J.* 1: 1177–8 (May 18), 1957.

A summary of a symposium on "Humane Technique in the Laboratory," organized by the Universities Federation for Animal Welfare, held at Birkbeck College, London, England, on May 8, 1957, Prof. P. B. Medawar, chairman. No details are given. (*See* Abstract 7: 107)

93. BEHNKE, A. R., GUTTENTAG, O. E. AND BRODSKY, C. Quantification of body configuration in geometrical terms. *U. S. Atomic Energy Comm. Doc.* USNRDL-TR-204, Dec. 1, 1957, 38 pp.

A formula is presented for the convenient translation of anthropometric measurements into geometrical relationships which in turn make possible an accurate physical description and classification of individuals. A geometrical model can be constructed which accurately represents individual body size and shape and the relationship between surface area and body volume. This model can be extended to depict interspecies relationships and hence is useful in radiobiology for interspecies comparisons. (*Nuclear Sci. Abstr.* 12: 6389 (May), 1958)

94. BERNSTEIN, L. AND ELRICK, H. The handling of experimental animals as a control factor in animal research—a review. *Metabolism* 6: 479–82 (Sept.), 1957.

A review of 13 literature references indicates that there may be striking changes in the albino rat as a function of handling or gentling. It is suggested that the variable of handling be made a standard procedure for both control and experimental animals in studies in which weight gain, skeletal length or reaction to stress is a dependent variable. (Condensed from author's summary)

95. BUTTLE, G. A. H., D'ARCY, P. F., HOWARD, E. M. AND KELLETT, D. N. Plethysmometric measurement of swelling in the feet of small laboratory animals. *Nature* 179: 629 (Mar. 23), 1957.

A plethysmometric device for measuring accurately the volumes of the feet of rats and mice is described. The apparatus consists of a modified 2-ml microburette connected to a 5-ml glass syringe. Anesthesia by i.p. injection with Sodium Amytal must be sufficiently deep to produce a completely flaccid leg and foot. The error of the method in 190 consecutive determinations amounted to 1.13%. By pretreatment with an i.v. injection of Evan's blue the location of the swelling may also be determined.

96. CHURCH, L. E. Combuthal as an anesthetic for baby chicks. *Poultry Sci.* 36: 788–91, 1957.

Combuthal, a combination of thiopentone and pentobarbitone, intraperitoneally administered to chicks, 1–7 days old, proved to be a satisfactory anesthetic without untoward aftereffects. The optimum dose for 1-day-old chicks was 0.05 ml and an additional 0.01 ml was needed in general for each additional day of age.

97. CLARKE, E. G. C. AND HAWKINS, A. E. Appraisement of total activity in laboratory animals. *Nature* 179: 1361 (June 29), 1957.

An apparatus is described which records all types of activity of small animals. The sensitivity to movement of the device can be varied. A trace for a single mouse in a standard cage is illustrated.

98. CLARKE, N. P., ZUIDEMA, G. D. AND SMITH, G. D. A method of producing controlled automatic inhalation anesthesia. *J. Am. Vet. Med. Assoc.* 130: 347–9 (Apr. 15) 1957.

A method of producing controlled automatic respiration and anesthesia in a wide variety of sizes of animals is described. The apparatus used was modified for animal use from an existing resuscitator and assistor. This machine has been used successfully in approximately 20 thoracic surgical procedures, using animals which varied in size from 80-gm hamsters to large dogs weighing 20–25 kg. The resuscitator was used alone, prior to the development of this apparatus, over a period of 5 yr. without requiring maintenance or repair.

99. CROFT, P. G. Aspects of anaesthesia. *Lab. Animals Bureau, M.R.C. Lab., Collected Papers* 6: 75–7, 1957.

Anesthesia is discussed from the aspect of humaneness in laboratory technique under the headings of administration, actions, and dangers.

100. DOBBERSTEIN, J. *Richtlinien für die Sektion der Haustiere.* (*Technique of Post-mortem Examination of Domestic Animals*) 8th ed. Berlin, Parey, 1957, 125 pp.

Post-mortem procedures are described for horse, cattle and small ruminants, swine, dog, cat, rabbit, beaver and fowl. Sample reports, methods for the determination of age, and measurements of the main organs are given.

101. DYCE, K. M. Veterinary radiology: The kidney. *X-ray Focus* 1: 2–3, 1957.

A brief account of intravenous pyelography and a double-contrast technique as applied to the dog. (*Vet. Bull.* 28: Abstr. No. 1206, 1958)

102. FARHI, L., OTIS, A. B. AND PROCTOR, D. F. Measurement of intrapleural pressure at different points in the chest of the dog. *J. Appl. Physiol.* 10: 15–8 (Jan.), 1957.

For the purpose of a study on the mechanics of breathing, intrapleural pressure was measured at 2 or more locations in 13 dogs, by using specially designed needles to insure patency and special wells to prevent inadvertent introduction of air into the pleural space.

103. FIELD, E. J. Anaesthesia in rabbits. *J. Animal Technicians Assoc.* 8: 47–8 (Sept.), 1957.

Experience in i.v. anesthesia in rabbits, based upon a series of 350 recovery and nearly 200 nonrecovery anesthetics, is presented. For all recovery operations Nembutal has been used with no supplementary inhalation anesthetic. For all nonrecovery anesthesia urethane was found most suitable. Since recovery from urethane is a prolonged process, the animal being incompletely restored to normal even after 36 hr., it is not a suitable anesthetic for relatively short operative procedures. The technique of administering anesthetics with recovery suitable for operations lasting about 2 hr., difficulties in albino rabbits and certain other breeds and their remedy, and a technique for administering anesthesia for prolonged nonrecovery experiments are described.

104. GRAZER, F. M. AND CLEMENTE, C. D. Developing blood brain barrier to trypan blue. *Proc. Soc. Exptl. Biol. Med.* 94: 758–60 (Apr.), 1957.

Trypan blue injected into developing rat embryos (10 days to birth) fails to stain the central nervous system. This impermeability in the developing central nervous system exists at the time when blood vessels invade the brain. It cannot be assumed, however, that the mechanisms which prevent protein-bound dyes from penetrating the cerebral blood vessels are the same for all other substances. (Author's summary)

105. HARVEY, D. G. On the routine chemical analysis of small volumes of urine. I. Review of methods. *Brit. Vet. J.* 113: 52–64 (Feb.), 1957.

After a general introduction concerning the range of tests the following methods of determination are reviewed: specific gravity of urine by means of the urinometer, approximate pH by means of indicator paper, protein by turbidity test, reducing substances by Benedict's or other tests, ketones by Rothera's nitroprusside reaction, blood by benzidine reaction and bile pigments by the methylene-blue test.

106. JORDAN, P. H., JR. AND SAND, B. F. A method for continuous intravenous infusion of dogs confined to cages. *Proc. Soc. Exptl. Biol. Med.* 96: 200–2 (Oct.), 1957.

A swivel assembly for continuous i.v. infusion of dogs confined to metabolic cages is described. Illustrations of individual portions of the swivel assembly and a schematic representation of the dog's connection to the swivel is included.

107. LABORATORY ANIMALS BUREAU, M.R.C. LABORATORIES. *Humane Technique in the Laboratory.* (*Collected Papers* vol. 6) London, 1957, 81 pp.

The symposium contains an abstract of "Humane techniques in the laboratory" by C. W. HUME; "The criteria for a humane technique" by P. G. CROFT; "The increase of humanity in experimentation: replacement, reduction and refinement" by W. M. S. RUSSELL; "Microorganisms in nutrition work" by G. SYKES; "Tissue cultures as substitutes for experimental animals" by F. K. SANDERS; "Machines as models" by W. G. WALTER. These papers stress the possibility of substituting lower organisms, *in vitro* and other assays for use of experimental animals.

For abstracts of other papers, see: Chance, M. R. A.; Croft, P. G.; Lane-Petter, W.; Lane-Petter, W. and Bloom, J. L.

108. LING, H. W. Anaesthesia in rabbits. *J. Animal Technicians Assoc.* 8: 58–60 (Dec.), 1957.

The precautions to be taken with the use of pentobarbitone, means of counteracting overdosage or individual intolerance, as well as the hazards of other anesthetics, such as ether, Pentothal and urethane, are discussed.

109. YOUNG, F. A. A primate control system *Proc. Animal Care Panel* 7: 127–37 (June), 1957.

A chair which may be used as a handling device as well as a restraining chair for monkeys is described and illustrated. The apparatus can be modified to suit special experimental purposes.

110. APTER, J. T. LSD-25 versus pentobarbital sodium. *Federation Proc.* 17: Abstr. No. 16 (Mar.), 1958.

Studies with 259 cats indicated that LSD-25 may be helpful in preventing death from barbiturate intoxication in laboratory animals.

111. BARNETT, M. The use of polythene for "Elizabethan" collars. *J. Animal Technicians Assoc.* 9: 50–2 (Dec.), 1958.

The construction of a restraint device for dogs, consisting of an "Elizabethan" collar made from Ziegler type polyethylene is described.

112. BLEICHER, N. Intramuscular Nembutal in canine anesthesia. *Vet. Med.* 53: 372 (July), 1958.

Intramuscular administration of Nembutal in canine anesthesia is recommended as being safer and simpler than i.v. or i.p. administration, especially in the hands of inexperienced personnel. Satisfactory dosages were found to be 20 mg/kg for premedication use, 30 mg/kg for basal anesthesia, and 40 mg/kg for general anesthesia. When employed as an anesthetic, opiate premedication is not needed. Overdosage is rare, but is readily detected and may be quickly corrected. (Author's summary)

113. CANDLIN, P. T. Trimar anesthesia for cats. *J. Am. Vet. Med. Assoc.* 132: 105–6 (Feb. 1), 1958.

Trichloroethylene (Trimar), administered with a special inhaler, provided an efficient, safe and simpler method of inducing anesthesia in cats. Rapid induction and recovery and greater control of the depth of anesthesia were the primary advantages of this procedure. (Author's summary)

114. CASE, R. W., BRUECKMAN, C. T. AND LORD, C. F., JR. A new technique for the preparation of sterile carcinogenic pellets for implantation in experimental animals. *Am. J. Hosp. Pharm.* 15: 565–6, 1958.

A practical method is described for the preparation of small sterile pellets of carcinogens for implantation into brains of laboratory animals. The method is simple and requires a minimum of time and equipment. This procedure is also being utilized to develop pellets of estrogens, androgens, etc. for delayed absorption and release. (Condensed from author's summary)

115. CHICK, E. W., EVANS, J. AND BAKER, R. D. The inhibitory effect of amphotericin B on localized *Rhizopus oryzae* infection (mucormycosis) utilizing the pneumoderma pouch of the rat. *Antibiotics & Chemotherapy* 8: 506–10 (Oct.), 1958.

Amphotericin B inhibited the hyphal development from spores of *Rhizopus oryzae* when introduced into the pneumoderma pouch

of a rat. The histological pattern, characterized by accumulation of macrophages, leukocytes, and giant cells with prominent tubercle formation and scar tissue, was essentially the same in untreated and treated rats. Amphotericin B appears promising as a therapeutic agent in the treatment of mucormycosis in man. The pneumoderma pouch of the rat affords an additional method for testing the effect of drugs on infectious disease agents. (Author's summary)

116. CLARKSON, T. B., BOYCE, W. H. AND KING, J. S. JR. A surgical technique for the formation of isolated pouches of the canine bladder. *Am. J. Vet. Research* 19: 661–5 (July), 1958.

A technique for the formation of bilateral isolated pouches of the canine urinary bladder is described. The enclosed mucosa remains histologically and histochemically normal for periods of 3 mo. after such isolation. Intravenous urography can be used to determine whether the pouches are completely isolated from the bladder proper. (Author's summary)

117. COKER, S. T. A note on a simple small animal respirometer. *J. Am. Pharm. Assoc., Sci. Ed.* 47: 686 (Sept.), 1958.

A simple inexpensive and easily constructed small animal respirometer suited especially for rats is described. It has been found useful in studying central nervous system and respiratory stimulants and depressants as well as muscle relaxants. (Author's summary)

118. COTTAM, S. M. AND HALLIDAY, R. Letter to the Editor. *J. Animal Technicians Assoc.* 9: 56 (Dec.), 1958.

Artificial respiration is easily and effectively applied by means of a rubber teat placed over the nostrils; the lungs are rhythmically inflated and deflated during approximately 15 sec. The method has proved 100% effective in reviving young rats, 2–3 wk. old, in which breathing had stopped completely during operation.

119. CUETO, C. AND BROWN, J. H. U. (With the Technical Assistance of RICHARDSON, A. P., JR.). Notes on technic. A rose Bengal-phloxine B stain for dog eosinophils. *Stain Technol.* 33: 95–6 (Mar.), 1958.

A new staining method for making routine counts of eosinophils in dogs was developed. A mixture composed of phloxine B 0.08 gm, rose bengal 0.02 gm, propylene glycol 50 ml and water 50 ml was used. Errors were reduced when the blood was collected without an anticoagulant such as heparin.

120. DOLOWY, W. C. AND HESSE, A. L. A combination restraint table and cassette holder for routine chest radiography in unanesthetized monkeys. *J. Am. Vet. Med. Assoc.* 133: 124–5 (July 15), 1958.

A method of restraining monkeys was devised in order to handle large groups of animals speedily and easily without exposing the attendants to dangerous levels of x-rays. A drawing of the combination restraint table and cassette holder is included.

121. ELRICK, H., BERNSTEIN, L., DIAMANT, E., WHITEHOUSE, J. M. AND BORDA-BOSSANA, D. Effects of handling on the adrenalectomized rat. *Proc. Soc. Exptl. Biol. Med.* 99: 696–8 (Dec.), 1958.

Young male Sprague-Dawley rats, subjected to bilateral adrenalectomy on the 21st and 23rd day of life, were handled daily, each time by a different investigator, 10 min/day for 2 mo. Handling consisted of holding the animal and stroking it repeatedly with the rat facing the handler. The experiments showed that a certain minimum level of adrenal hormones is necessary for the enhancing action of handling on weight gain, efficiency of food utilization, maze learning ability and resistance to thiourea toxicity previously reported in the normal young albino rat. It was not yet determined whether the effects of handling depend on presence of adrenal medullary and/or adrenocortical hormones.

122. EPSTEIN, S. S. (With the Technical Assistance of BREACH, G. D.). An intra-oral inoculation technique for the production of experimental pneumonia in mice. *J. Hyg.* 56: 73–9 (Mar.), 1958.

Techniques for the production of experimental pneumonia are briefly reviewed. A new method of intraoral inoculation in the anesthetized mouse is described and its advantages with particular reference to the danger of aerial contamination and facility of technique are discussed. The time required to inoculate 1 mouse is less than 1 min. and recovery from anesthesia commences in a similar period of time after which the animal can be returned to its cage. An application of this method to virulence studies is indicated and other possible applications suggested. (Author's summary modified)

123. EPSTEIN, S. S. AND STRATTON, K. (With the Technical Assistance of BREACH, G. D.). Further studies in the mouse intra-oral inoculation technique. *J. Hyg.* 56: 80–3 (Mar.), 1958.

The differential dispersal of an inoculum delivered to anesthetized mice by 2 methods was compared by means of a radioactive tracer technique. The results clearly show that the intraorally inoculated animal accepts a larger proportion of the total volume inoculated and that a significantly higher fraction of this reaches the lungs than in mice inoculated by the intranasal technique. (Author's summary modified)

124. FIELD, L. W., DE GRAAF, W. AND WALLIS, A. T. Constant output blood perfusion pump for use in cross transfusion experiments in small laboratory animals. *J. Appl. Physiol.* 12: 142–4 (Jan.), 1958.

A pump, which acts by movement of a diaphragm by a hydraulic medium, is described. The pump delivers from 1–6 ml blood/min., with flow-rates remaining constant over a wide range of inflow and outflow pressures, and with little damage to cellular elements. It has been used in 20 rabbits and more than 150 rats. Experiments using rats run consistently for 4–5 hr. and those using rabbits for over 5 hr.

125. FRAZER, S. C. Laboratory trial of a paper strip test for proteinuria. *Brit. Med. J.* 1: 981–3 (Apr. 26), 1958.

A simple and speedy test for proteinuria, using albustix strips, is described. The test appears adequately sensitive for routine use. Variation of urine acidity or alkalinity within physiological limits does not interfere with the results qualitatively, but it slightly affects the quantitative indication. Gross alkaline fermentation of urine can lead to spurious positive indications, while the addition of acid or toluene as preservatives can lead to false-negative reactions. (Author's summary modified)

126. FREDRICKSON, T. N., CHUTE, H. L. AND O'MEARA, D. C. A simple improved method for drawing blood from chickens. *J. Am. Vet. Med. Assoc.* 132: 390–1 (May 1), 1958).

An improved method of venipuncture, requiring a 20-gauge hypodermic needle, 1.5 in. long, and a 5-mm glass syringe, is

described for application in birds older than 5 wk. The method proved satisfactory in a study involving over 500 birds. It was particularly efficient for one operator working alone. The technique was used for drawing blood from birds on the range, in poultry houses and in the laboratory.

127. GRAZER, F. M. Technic for intravascular injection and bleeding of newborn rats and mice. *Proc. Soc. Exptl. Biol. Med.* 99: 407–9 (Nov.), 1958.

An intracardiac technique for bleeding and injection of newborn rats and mice is described. This technique provides several advantages over the i.v. route. It can be performed by one person without assistance and without much previous experience. There are no postinjection hematomas and no pressure need be applied after withdrawal of the needle.

128. GROSS, P. A self-retaining illuminated laryngoscopic speculum for intratracheal procedures. *A.M.A. Arch. Ind. Health* 18: 429–30 (Nov.), 1958.

A simple apparatus of the "do it yourself" type is described which permits performing as many as 60 intratracheal injections/hr. Some rats were given up to 10 intratracheal injections in 7 mo. by this method without obvious manipulative traumata. The illuminated laryngoscopic speculum which may be used for all small animals is self-retaining and combines the function of a mouth gag and tongue depressor. With the speculum in position the vocal cords are easily visualized and intratracheal manipulations are readily accomplished. (Author's summary modified)

129. GUEST, G. M., MACKLER, B. AND ROBERTS, J. R. Apparatus for continuous intravenous infusion in dogs. *Proc. Soc. Exptl. Biol. Med.* 98: 540–2 (July), 1958.

A simple apparatus for continuous i.v. infusion of fluids in dogs, employing a standard assembly of reservoir bottle and flexible connecting tubing that leads to the dog's harness, and a plastic catheter dwelling in an external jugular vein is described. Suspension of the apparatus by a swivel above the dog's cage permits the dog almost complete freedom of movement during long periods of continuous infusions. (Author's summary)

130. HANSSON, C.-H. Anaesthesia in the dog using short-acting barbiturate and nitrous oxide supplemented with succinylcholine iodide and positive-negative artificial respiration. *Nord. Veterinärmed.* 10: 407–25, 1958.

Dogs were given morphine, scopolamine and atropine as preanesthetic agents. Anesthesia was then induced by a short-acting barbiturate, maintained by nitrous oxide and muscular relaxation was achieved by succinylcholine. Artificial respiration was administered by means of an automatic positive-negative pressure apparatus.

131. HANSSON, C.-H. AND JOHANNISSON, D. Inhalation anaesthesia with automatic artificial respiration during succinylcholine relaxation in large animals. *Nord. Veterinärmed.* 10: 469–86, 1958.

A circle-circuit anesthesia apparatus combined with an automatic respirator for horses and cows has been constructed. About 70% nitrous oxide has proved to give sufficient anesthesia in both horses and cows. After premedication with atropine and induction with a short-acting barbiturate, nitrous oxide has been used as anesthetic agent and succinylcholine as muscle relaxant (BNS-anesthesia), respiration being maintained artificially with the above mentioned apparatus. BNS-anesthesia has not been found to be suitable in horses. In cows the method has given promising results and seems to be suitable particularly at operations of long duration when complete muscle relaxation is wanted. (Author's summary)

132. HANSSON, C.-H. AND OBEL, N. A method for recording blood pressure during operation. *Nord. Veterinärmed.* 10: 457–68, 1958.

Arterial blood pressure in animals during therapeutic operations is recorded by introducing a fine polythene catheter into an artery perfused with Ringer's solution at a constant low rate, with a side connection leading to a mercury manometer. The pressure changes are converted to potential changes which can be recorded by an electronic compensator. The method has been found to be quite reliable for periods up to 5 hr. The compensator can be calibrated to give a blood pressure curve in a form which can be read from any point in the operating room. The method was applied to dogs, horses and cattle.

133. HARTLEY, J. L. AND HARRIS, N. O. A comparative evaluation of tissue tolerance to a gallium alloy. *U. S. Air Force, School of Aviation Medicine Rept.* 58–148, Nov. 1958, 9 pp.

A 1.3% solution of pentobarbital sodium administered i.v. (1 ml/lb. body wt) was used as an anesthetic for guinea pigs.

134. HINT, H. C. AND RICHTER, A. W. A simple intravenous infusion technique for mice. Method and some applications. *Acta pharmacol. toxicol.* 14: 153–7 (Feb.), 1958.

The infusion was made into inbred white mice from a strain from Statens Seruminstitut, Copenhagen, through a thin, flexible polyethylene catheter, connected by means of the sharp cutoff end of a 22-gauge injection needle to a tail vein. The animal moved freely in a glass cylinder during infusion. On continuously infusing at a fixed rate adequate concentrations of the test solution, typical symptoms or end points may be observed at different dose levels. Examples are given of determinations of LD_{100} and of quantitative estimations of anticonvulsive drugs.

135. HIRSCH, S. Metal-tipped plastic intravenous needle. *Am. J. Surg.* 95: 853 (May), 1958.

A flexible needle for intravenous therapy, which can be sterilized by autoclaving, boiling, or immersion in antiseptic solutions, is described. It is made of Teflon tubing, gauge 18 (or size desired), attached to a metal tip for easy insertion, and completed with a Luer hub. It may be left in the vein for several days.

136. KNIAZUK, M., MARTIN, W. R. AND UNNA, K. R. A new method of measuring movement in small animals. *J. Pharmacol. Exptl. Therap.* 122: 38–9A (Abstr.) (Jan.), 1958.

An activity cage consisting of a 30,000-cps. crystal oscillator radiating sound into a cylindrical Plexiglas cage is described. The instrument is capable of detecting the movement of small objects and small movements, such as the respiratory movements of a mouse.

137. LEACH, L. J. AND SPIEGEL, C. J. An animal inhalation exposure unit for toxicity screening. *Am. Ind. Hyg. Assoc. J.* 19: 66–68 (Feb.), 1958.

To expose a relatively large number of animals for a 5-yr. study of the inhalation of uranium dioxide, 4 separate chambers of the hexagonal type have been combined to operate from a common air intake and dust feed system. The animal capacity of the new unit is 16 monkeys, 32 beagle dogs and 160 rats. The exposure unit has been in operation for approximately 2½ yr.; performance has been satisfactory. The atmospheres in the 4 chambers are, for most practical purposes, identical in dust con-

centration and particle-size distributions. While the new unit was designed primarily for a long-term study with large numbers of animals, it may be modified easily for other types of inhalation experiments. By separate control of individual dust inlets, 4 different concentrations of the same compound or 4 different compounds could be tested simultaneously. (Author's summary)

138. Liuzzo, J. A., Reineke, E. P. and Pearson, A. M. Determination of specific gravity by air displacement. *J. Animal Sci.* 17: 513–20 (Aug.), 1958.

A technique was developed for the determination of body volumes and specific gravity of living animals by air displacement; the apparatus used is described. Experiments were made with guinea pigs. Comparisons with the water displacement method showed that the air displacement was less accurate.

139. Llaurado, J. G. A method for rapid adrenalectomy in the rat. *J. Animal Technicians Assoc.* 8: 75–78 (Mar.), 1958.

A method for bilateral adrenalectomy is described which is based on close collaboration between the operator and his assistant. The whole procedure from the commencement of anesthesia until the rat is back in its cage requires less than 4 min. Ether anesthesia is maintained by the "open drop" technique with the rat fastened on a cork board. Both young rats, about 1 mo. old, and adult ones have been adrenalectomized. In adult rats the existence of adipose globules may be confused with the adrenal; determination of the consistency of these globules, however, will dispel any doubt.

140. McCormick, J. A. Radiosiotopes in animal physiology. A selected list of references. *Technical Information Service Extension, AEC* TID-3315, Dec. 1958, 118 pp.

This bibliography contains 2439 references on uses of radioisotopes in metabolite physiology in animals, nonmetabolite physiology in animals, injurious agent physiology in animals, and general physiology in animals. The references were selected from scientific journals published during 1948–1957. A list of the periodicals from which the references were selected and an author index are included. (*Nuclear Sci. Abstr.* 13: Abstr. No. 11537, 1959)

141. Maykut, M. O. Studies on degeneration of myelin sheaths of nerves caused by long-acting local anesthetics injected subcutaneously into guinea pigs. *Can. J. Biochem. Physiol.* 36: 511–6 (June), 1958.

The neurological changes induced by preparations of long-acting local anesthetics and their components on cutaneous nerves, following a s.c. injection into the backs of guinea pigs were studied. Some of the materials tested caused generalized inflammatory reactions in the skin and s.c. tissue but little specific injury to the nerves; others caused greater degrees of nerve injury, with little inflammatory reaction. Two kinds of nerve injury are apparent: edema and destruction with Wallerian degeneration, with or without edema. The rate of nerve regeneration appears to determine the duration of anesthesia, only a few fibers being necessary for the return of sensation. The materials which tend to approach the ideal long-acting local anesthetic are procaine amide, procaine-Nembutal combination product, procaine base and Cyclaine. (From author's summary)

142. Meltzer, M. R. and Folk, G. E., Jr. A method for correlating bladder emptying and total activity in rodents. *J. Mammalogy* 39: 454–5 (Aug.), 1958.

An inexpensive apparatus has been designed and used for the simultaneous recording of bladder emptying and total activity displayed by rodents. The animal is housed in a galvanized can which is placed between 2 pieces of mesh serving as the top and bottom of the cage. A graduated tube is attached to the cage allowing for the measurement of water consumption. Food pellets may be left inside the cage. Upon urination, the urine flows through a plastic funnel and over a glass bulb which pinpoints the sample on the sloped rim of a revolving paper plate. A simple modification of the equipment makes it possible to collect the urine for analysis.

143. Naess, K. and Rasmussen, E. W. Approach-withdrawal responses and other specific behaviour reactions as screening test for tranquillizers. *Acta Pharmacol. Toxicol.* 15, No. 2: 99–114, 1958.

A new procedure using small laboratory animals in conflict-induced situations is described as a screening test for drugs with sedative effects of different types, particularly tranquilizers. Shock was induced in rats by an electric shock apparatus in which each time the rat tries to drink, the circuit closed and the animal got a shock. After the rats had become accustomed to the apparatus, they were injected subcutaneously with the drug to be tested (benactyzine hydrochloride, chlorporomazine hydrochloride or meprobamate, respectively) while controls were given NaCl as placebo preparation. A total of 6,765 behavior reactions (approach-withdrawal response) in 198 rats (70 of them controls) were recorded and the results were statistically evaluated. The method not only reveals whether a drug has a tranquilizing effect but also permits differentiation between psychic effects.

144. Panchenko, L. F. A modified pressure chamber for use in a small laboratory. *Byull. Eksptl. Biol. Med.* 45, No. 1: 120–1 (Trans. 125–6), 1958.

A modification of a pressure chamber, convenient for work with rabbits, cats and guinea pigs is proposed. A vacuum drying cabinet of VSh-0035M type was used for the equipment of the pressure chamber. The rapidity and the degree of air rarefaction was registered in a chamber by 3 instruments: by a vacuum meter with a pointer, a membrane variometer and an aneroid altimeter. A special inspection window permits observation of the behavior of laboratory animals. (Author's summary)

145. Roddick, B. J. A one-man sheep-bleeding technique. *New Zealand Vet. J.* 6: 20, 1958.

The sheep was placed in the sitting position, supported by the right leg of the operator. The head and neck were bent to the left of the animal and downwards by the operator's left hand. This exposed and distended the jugular vein and also immobilized the animals, so that a hypodermic needle attached to a syringe could be inserted by the right hand. R. stated that 20–25 sheep could be bled in half an hour by this method. (*Vet. Bull.* 29: Abstr. No. 591, 1959)

146. Watson, D. and Pratt, D. A. H. Estimation of blood-urea. A rapid micro method. *Lancet* 2: 1088–9 (Nov. 22), 1958.

A new quick method for the determination of urea is described. This is a simple spot test suitable for use with as little as one drop capillary blood, urine, or other body fluid. The method makes use of a soybean meal suspension, a filter paper treated with manganese and silver nitrate, and a hot-air oven. There is good correlation between the values obtained by this procedure and that of Archer and Robb. Estimations on blood to which varying amounts of urea have been added show a satisfactory recovery. The cost of the procedure in reagents and technicians' time is about a quarter of that of conventional methods. (Author's summary)

147. Willard, D. H., Blair, W. J., Temple, L. A. and Smith, V. H. Techniques for exposure of mice to aerosols

of radioactive particles. *U. S. Atomic Energy Comm. Doc.* No. HW-52368, Nov. 1, 1958.

An exposure chamber, glove box, radioactive particle generators and auxiliary equipment for respiratory exposures of mice to atmospheres of radioactive particles are described. Methods for exposing mice to radioactive aerosols as dust or as particles suspended in fog are also presented with data from typical experiments demonstrating the relative merits of the techniques. The design of the equipment emphasizes safe administration of radioactive aerosols to mice. (Author's summary)

148. ANONYMOUS. Transistor electrocardiograph marker. *Am. J. Vet. Research* 20: 927 (Sept.), 1959.

The Taber Model 202G Electrocardiograph QRS Marker, manufactured by Taber Instrument Corp., is described. It will amplify 1 millivolt heart voltages to 0.5 volt.

149. ANONYMOUS. Demand-breathing respirator. *Am. J. Vet. Research* 20: 928 (Sept.), 1959.

An intermittent positive-pressure respirator (Bird Residual Breather Mark 7, manufactured by Instrumentation Assoc.) which assists breathing under abnormal conditions, is described.

150. ARABEHETY, J. T., DOLCINI, H. AND GRAY, S. J. Sympathetic influences on circulation of the gastric mucosa of the rat. *Am. J. Physiol.* 197: 915–22 (Oct.), 1959.

A method is presented for quantitatively evaluating the gastric mucosal blood content in rats by densitometric measurement of the India ink content of the mucosa following the intraaortic injection of India ink in the living animal. (From author's summary)

151. ARONSON, A. L. AND GANS, J. H. The narcotic analgesics and their antagonists as adjuncts to barbiturate anaesthesia. II. Clinical applications. *J. Am. Vet. Med. Assoc.* 134: 459–63 (May 15), 1959.

The preanesthetic administration of morphine or meperidine (Demerol) in suitable doses significantly reduced the amount of pentobarbital sodium required to attain plane 2 surgical anesthesia. Hypoventilation and circulatory depression were overcome by the use of the narcotic antagonists without altering the plane of anesthesia. One mg of nalorphine is recommended per 10 mg of morphine or 20 mg of merperidine used preanesthetically. One mg of levallorphan is recommended per 50 mg of morphine or 100 mg of merperidine. The antagonist may be administered immediately after the induction of anesthesia, when signs of hypoventilation appear, or in fractional doses during surgery and the recovery period. (Author's summary)

152. BARCLAY, W. R., BRUCE, W. R. AND FARID, Z. A simplified rabbit ear chamber. *A.M.A. Arch. Pathol.* 68: 409–12 (Oct.), 1959.

The rabbit ear chamber technique offers a unique method for studying the circulation of living tissue, also the course of infections, the growth of tumor cells, etc. The chamber is easily assembled from a sheet of polyvinyl, some Teflon and Lucite rods with stainless steel expansion rings. Placement of the chamber in the ear requires the punching of only one hole and stripping of the skin off cartilage on one side of the ear. The chamber is then filled with saline. Blood vessels will grow through the holes of the chamber, vascularize in 4 wk. and the tissue is fully mature and suitable for experiments within 6 wk.

153. BINNS, W. AND JAMES, L. F. A plastic rumen fistula apparatus for sheep—Its insertion and use. *J. Am. Vet. Med. Assoc.* 135: 603–5 (Dec. 15), 1959.

A plastic rumen fistula apparatus can be inserted into sheep in one operation. Such fistulas facilitate the force feeding of large quantities of unpalatable substances in exact daily doses. Large quantities of any substance may be fed quickly. Plant material can be ground, mixed with water to a creamlike consistency, and introduced deeply into the rumen through a funnel. (Author's summary)

154. BLAKESLEE, H. N. AND IVES, M. A restraining box for monkeys. *Toxicol. and Appl. Pharmacol.* 1: 443–5 (July), 1959.

A restraining box was designed by means of which the feeding time required under ordinary laboratory conditions was reduced by 80% with only one suffocation experienced in some 13,000 feedings. A technique for placing the monkey into this box is also described.

155. BRADY, J. V. Animal experimental evaluation of drug effects upon behavior. In: *Association for Research in Nervous and Mental Diseases: The Effect of Pharmacologic Agents on the Nervous System.* Baltimore, Williams & Wilkins, 1959, Chapt. 9, pp. 104–25.

Techniques were developed for reliably producing and selectively measuring emotional behavior patterns in experimental animals such as rats and monkeys and for investigating the effects of tranquilizers and other drugs upon the emotional behavior of the animals. (Also under the title "A comparative approach to the study of drug effects on the behavior of higher animals." In: BASS, A. D., ed. *Evolution of Nervous Control from Primitive Organisms to Man. (Am. Assoc. Advance. Sci. Publ.* 52: 115–33) Washington, D.C., 1959.)

156. BROŽEK, J. Experimental studies on the impact of deficient diet on behavior. *Borden's Rev. Nutrition Research* 20: 75–88 (Nov.–Dec.), 1959.

Methods for laboratory study of behavior as related to deficient diets are discussed. (154 references)

157. BURCH, G. R. Sheep drenching technique. *J. Am. Vet. Med. Assoc.* 135: 622–3 (Dec. 15), 1959.

The 3 common methods for administering liquids to sheep are rapid oral drenching, slow oral drenching and the esophageal tube technique. The 3 techniques were tested with 9 sheep, using a dyed 15% suspension of diphenthane-70. Lambs drenched by the slow or rapid technique had the suspension in the abomasum; when the esophageal tube was used, the medication was found in the reticulum.

158. CASTOR, G. B. A simple plastic arterial cannulation device which minimizes clotting. *J. Appl. Physiol.* 14: 137 (Jan.), 1959.

A description and diagram of the plastic cannulating device is furnished. The device was used on 50 cats and the test had to be interrupted only in 2 cases because of clotting while with glass cannulas clotting occurred in 26 out of 50 cats.

159. DOLOWY, W. C. AND HESSE, A. L. Chlorpromazine premedication with pentobarbital anesthesia in the rabbit. *J. Am. Vet. Med. Assoc.* 134: 183–4 (Feb. 15), 1959.

The preanesthetic use in New Zealand white rabbits of i.m. chlorpromazine hydrochloride in doses ranging from 25 to 100 mg/kg of body wt., followed by 20 mg/kg of pentobarbital sodium given i.v., results in a more tractable animal in which to give the i.v. anesthetic and a much longer duration of surgical anesthesia. (Condensed from author's summary)

160. EDWARDS, G. A., EDWARDS, C. H. AND GADSDEN, E. L. An inexpensive metabolism apparatus for collecting CO_2, excreta and blood from small experimental animals. *International J. Appl. Radiation and Isotopes* 4: 264–6 (Jan.), 1959.

The apparatus described and illustrated permits *1*) intermittent and quantitative collection of expired CO_2, *2*) withdrawal of blood samples at specific times during the experiment and *3*) intermittent collection of urine and feces. In experiments with rats 10 or more samples were obtained during a 24-hr. interval.

161. EDWARDS, J. W., SLOAN, R. F., BLEICHER, N. AND ASHLEY, F. L. An ether chamber for small laboratory animals. *Proc. Animal Care Panel* 9: 71–3 (June), 1959.

An ether chamber for anesthetizing many small laboratory animals simultaneously, quickly, and safely has been described. Construction is of Lucite and a valve arrangement allows a constant flow of air and vaporized ether. This chamber is considered to be safer, cleaner, and easier to use than present methods. (Author's summary)

162. EISEN, L. AND ZEIGEN, R. S. A supine seat for high-stress testing of primates. *WADC Tech. Rept.* 59–165, April, 1959, 18 pp.

A supine seat and restraint harness, with surrounding inclosure, for tests with a *Macaca cynomolgus* monkey (*Macaca iris*) under various abnormal stresses is described. With minimum modification this supine seat and restraint harness could be used for ground tests or experiments with primates in space flight. A brief description of an earlier supine seat and restraint harness with a squirrel monkey is included. (From author's summary)

163. FREEMAN, W. J. An ergometer for measuring work from cats as an index for drive. *J. Appl. Physiol.* 14: 1071–2 (Nov.), 1959.

Drive, which is an internal state of reactivity, is measured indirectly by determination either of an antecedent stimulus or of the magnitude of the physiological or behavioral response associated with the drive. The device described was used to measure on a continuous scale the amplitude of the response in a cat, that is, how fast and how hard a cat will work to reach a specified goal.

164. GADDUM, J. H. *Pharmacology*. 5th ed. New York, Oxford Univ. Press, 1959, 587 pp.

The action of drugs and a number of elements on the various organs and on functional and metabolic processes is discussed. Experimental methods for the study of the action of these substances are included under most organs or systems covered. Among techniques described, are the following: biological assays, assays for vitamins, androgens, estrogens, methods using radioactive isotopes, various means of anesthesia, study of purgatives, diuretics, toxicity tests, etc. In Chapter 16, "Respiration," a diagram shows average values for the following respiratory constants in mouse, rat, guinea pig, rabbit, cat, dog, horse and man: total air breathed, rate of respirations, O consumption, CO_2 production, tidal air per min.

165. GAFFORD, R. D. AND CRAFT, C. E. A photosynthetic gas exchanger capable of providing for the respiratory requirement of small animals. *U.S. Air Force School of Aviation Medicine Rept.* No. 58–124, Jan., 1959.

The method described is based on the photosynthetic mechanism of green plants by which CO_2 and H_2O are converted to organic carbohydrate and molecular O_2. Two strains of algae, a green and a blue-green alga have been used for the photosynthetic system and a photosynthetic gas exchanger capable of producing 10 l O_2/day has been designed. The device can provide O_2 for, and take up CO_2 from, 4 30-gm mice on a continuous basis.

166. GALE, D. AND JACK, A. A mouse autopsy board. *Tech. Bull. Registry Med. Technologists* 29: 31–2 (Feb.), 1959.

An autopsy board for mice, made of hard wood and able to withstand repeated autoclaving without splintering or disintegrating, is described. A similar board made on a larger scale can be used for rats and guinea pigs.

167. HALBERG, F., ALBRECHT, P. G. AND BITTNER, J. J. Corticosterone rhythm of mouse adrenal in relation to serum corticosterone and sampling. *Am. J. Physiol.* 197: 1083–5 (Nov.), 1959.

A method for measuring adrenal activity in mice is described. Male mice of the B_1 strain were used. The influence of the physical environment, such as light, is demonstrated. It is concluded that the daily peak of corticosterone in mouse adrenals can probably be shifted to any desired clock hour by appropriate manipulation of the lighting regimen.

168. HALL, C. E., HALL, O. AND ADAMS, A. R. An electromechanical apparatus for stressing small animals. *J. Appl. Physiol.* 14: 869–70 (Sept.), 1959.

A grid-floored cage system suitable for stressing large numbers of small animals was described. The cage system embodies a compensator circuit which prevents fecal accumulations from constituting an effective short circuit. The apparatus may be used to administer either constant voltage or constant currents. The usefulness of the device for discontinuously applied stress is not limited by the lack of provision for food or water for the animals. With rats the duration of current flow for individual shocks must be short since they tend to bite the rods which may cause convulsions and compression fractures of the spine. The stress obtained is easily quantitated and controlled and does not produce direct visible tissue damage.

169. HOWELL, C. D. AND HORVATH, S. M. Reproducibility of cardiac output measurements in the dog. *J. Appl. Physiol.* 14: 421–3 (May), 1959.

A method for the measurement of cardiac output in dogs is described.

170. LUMB, W. V. Closed-circuit halothane anesthesia in the dog. A report of 142 anesthetic periods. *J. Am. Vet. Med. Assoc.* 134: 218–21 (Mar. 1), 1959.

A clinical study of halothane anesthesia in the dog was undertaken; 142 anesthetic periods were conducted with the drug and various surgical operations performed. It proved to be a potent anesthetic agent, producing satisfactory anesthesia and muscle relaxation. One dog in the series died. (Author's summary)

171. McKennis, Q. S., Bowman, E. R. and McKennis, H., Jr. A constant-rate infusion apparatus. *Toxicol. and Appl. Pharmacol.* 1: 61–4 (Jan.), 1959.

An apparatus, assembled from inexpensive commercial components, for simultaneous i.v. infusion at constant rate to 6 or more animals, is described.

172. Markowitz, J., Archibald, J. and Downie, H. G. *Experimental Surgery*. 4th ed. Baltimore, Williams & Wilkins, 1959, 931 pp.

The book contains the following chapters: the antivivisection movement; care and feeding of animals; anesthesia; equipment, technique, sutures and instruments; surgical exercises; standard technical procedures in the surgery of the alimentary canal; gastric fistulae; intestinal fistulae: jejunostomy; the experimental production of chronic peptic ulcer; exteriorization of an intestinal loop; surgical physiology of intestinal obstruction; absorption, excretion and motility of the small intestine and colon; experimental surgery of the esophagus; some features of experimental peritonitis; experimental surgery of the pancreas; total biliary fistula; experimental surgery of the gall bladder; transplantation of ducts; fascial transplantation; transplantation of organs; experimental surgery of joints; the experimental surgery of bone; hypophysectomy in dogs; experimental surgery of the lung, trachea and bronchi; experimental surgery of the heart; the mechanical heart: cardiac arrest; experimental surgery of the involuntary or autonomic nervous system; vascular surgery; experimental hematology, factors governing restoration of plasma protein; experimental surgery of the kidney; the experimental surgery of the liver; the experimental surgery of the prostate; hibernation and hypothermia; central nervous system.

173. Mason, W. A. Development of communication between young rhesus monkeys. *Science* 130: 712–3 (Sept. 18), 1959.

An apparatus for the investigation of communication between rhesus monkeys is described. Six pairs of about 18-mo.-old rhesus monkeys, born in the laboratory and removed from the mother at birth, were used in the food-sharing tests. The communication situation was based on the response of an operator monkey to cues provided by an informant monkey which indicated the location of food. Performance under the test conditions improved progressively to levels consistently above chance.

174. Mishkin, M., Gunkel, R. D. and Rosvold, H. E. Contact occluders: A method for restricting vision in animals. *Science* 129: 1120–1 (May 1), 1959.

Preliminary observations show that contact occluders can be used to produce temporary "blindness" in monkeys. This report also describes how such occluders can be made. (Author's summary)

175. Nakayama, F. Metabolic relationship of exogenous phospholipids and phosphate to biliary phospholipids. *Am. J. Physiol.* 196: 319–24 (Feb.), 1959.

A glass tube was devised to hold the right hind leg of the rat or dog in position for continuous bile drainage.

176. Noyes, H. E. A chronic irradiation source for small animals. *Radiation Research* 10: 400–1 (Apr.), 1959.

A simple chamber, consisting of 2 pieces of double-thickness glass embedded in lead, has been designed for chronic irradiation of small animals. The animals are placed on a stainless steel pan, 22 in.^{2} and 8 in. deep, which will house 60 mice or 15–20 rats or guinea pigs.

177. Ormiston, D. W., Rohles, F. H., Jr. and Grunzke, M. E. A device for measuring gross motor behavior in primates. *Wright-Patterson Air Force Base, WADC Techn. Note* 59–353, Oct., 1959.

To meet the need for a method of measuring gross motor behavior as affected by various gravitational forces, a jumping device for primates was developed consisting of a large box with a stand at each end and a well in the middle. The well carried a constant electrical charge. Shock, preceded by a tone, was used to make the animal jump over the well to the opposite side. Motion pictures of the jump, as viewed through the Plexiglas side and top, allowed measurement of the height and distance of the jump. Other possible uses of the device are discussed. (Author's summary)

178. Renaud, S. Improved restraint-technique for producing stress and cardiac necrosis in rats. *J. Appl. Physiol.* 14: 868–9 (Sept.), 1959.

A typical alarm reaction was produced within a few hours in rats weighing 90–100 gm by restraining the animals to a board whereby the paws were attached to brackets by means of adhesive tape. A diagram of the restraint board is given. The alarm reaction was characterized by enlargement of the adrenals, thymicolymphatic involution and occurrence of gastric ulcers. After 24 hr. restraint and without any other treatment cardiac necrosis is rarely visible. However, large patches of cardiac necrosis appeared after a 7-hr. period of restraint if pretreatment with NaH_2PO_4 plus certain corticoids was given.

179. Rohles, F. H., Jr. and Coy, R. A miniaturized operant conditioning chamber for behavioral research in the upper atmosphere. *Wright-Patterson Air Force Base, WADC Techn. Note* 59–261, 1959, 7 pp.

The basic components of the unit are a lever that the mouse presses to obtain food, a magazine for holding food pellets, a feeder mechanism, a light for the feeder compartment and a programming unit. The mouse is required to press the lever on a fixed ratio schedule of 25:1 for 20 min. out of every 6 hr. for food reward. The chamber utilizes mechanical power and response recording is compatible with telemetry systems. The unit is 3.5 in. in diameter, 6.5 in. long and weighs about 2.25 lb. Plans are in process to modify this unit for larger species.

180. Rosenberg, A. J. and Rude, F. R. Short cuts in hematology. *J. Am. Vet. Med. Assoc.* 135: 506 (Nov. 15), 1959.

A disposable sterile, empty cartridge-needle unit can be used for obtaining and storing blood. For the purpose of heparinization a small amount of heparin solution can be drawn into the cartridge-needle unit and then ejected whereby enough heparin remains on the inner surface of the cartridge and in the lumen of the needle to prevent clotting without increasing the volume of blood significantly. Simple procedures for cleansing slides and cell-counting pipettes are proposed. Other short cuts suggested are the use of a vibrator-type, electric-powered pipette shaker and a hand talley counter for rapid leukocyte, erythrocyte and differential counts.

181. Rosenthal, S. R., Spurrier, W. A. and Trahan, H. A new mouse-scalding technique for long-term experiments with preliminary serologic studies. *Federation Proc.* 18: Abstr. No. 1982 (Mar.), 1959.

A stainless steel mesh (no. 64) basket is so shaped that the bottom accepts the curvature of the back of the mouse and the ends tilt upwards so that the urethra and anal orifices on one end and the head and ears on the other are at a level above the anterior axillary lines. Lateral stainless steel arms project from the basket

in such a manner that when the preparation is set into a water bath, the back of the mouse up to the post axillary lines is submerged into the water. The LD_{50} for clipped mice 18–20 gm was 8 sec. at 70°C. With complete healing of the skin of survivors (4 mo.), their sera reacted with rat skin "burn toxin" rabbit antisera (hemoagglutinins and hemolysins). Autoimmunization following thermal injury to the skin thus occurs in the mouse as well as in the rat. The antigens from both species of animal are thus related. The basket technique reported minimizes complications arising from scalding of anus or urethra.

182. SALERNO, R. A. A new technique for thoracotomy and chest closure in the experimental animal. *J. Thoracic Cardiovasc. Surg.* 38: 97–103 (July), 1959.

A new technique of thoracotomy in which retraction of muscle and fascia is the predominant feature was used in over 150 dog operations without a single wound complication. The method is quick and easy and avoids unnecessary blood loss and trauma.

183. SCHAFFENBURG, C. A. Device to control constriction of main renal artery for production of hypertension in small animals. *Proc. Soc. Exptl. Biol. Med.* 101: 676–7 (Aug.-Sept.), 1959.

An instrument has been constructed which permits accurate control of degree of constriction of the main renal artery in small animals such as rats, and which facilitates production of acute and chronic hypertension in a high percentage of such animals of equal weight.

184. SCHLANG, H. A. A simple cross transfusion and perfusion pump for small animals. *J. Lab. Clin. Med.* 54: 163–6 (June), 1959.

A simple, easily made glass perfusion pump is described. The pump is activated by changes in air pressure within the pump body induced by a clinical syringe. Flow direction is controlled by flutter valves made of dental dam. The construction of the flutter valves is given in detail since the method eliminates many of the difficulties usually involved and is applicable to the construction of fine flutter valves for a variety of purposes. (Author's summary)

185. SCHMIDT, H., JR. AND MOAK, S. J. Some drug effects influencing barbiturate facilitation of water ingestion. *Am. J. Physiol.* 196: 307–10 (Feb.), 1959.

Pentobarbital anesthesia in combination with chlorpromazine and a stimulant barbiturate (5 ethyl, 5,1,3,dimethyl-2-butenyl barbituric acid) was studied in female albino rats with respect to water intake of the animal.

186. SHOEMAKER, W. C., WALKER, W. F., VAN ITALLIE, T. B. AND MOORE, F. D. A method for simultaneous catheterization of major hepatic vessels in a chronic canine preparation. *Am. J. Physiol.* 196: 311–4 (Feb.), 1959.

A feasible method for measuring concentration changes of various substances as they enter and leave the liver is described together with the operative technique. This preparation allows simultaneous sampling of blood from all major hepatic vessels in the *in vivo*, unanesthetized dog under chronic experimental conditions. A modification of this technique is described whereby liver biopsies may be obtained at the same time as the blood sampling. (Author's summary)

187. SIMMONS, V. P. A technique for handling rabbits (motion picture). *Federation Proc.* 18: Abstr. No. 1759 (Mar.), 1959.

A silent motion picture demonstrating a technique whereby it is readily possible for 1 person, without the need of any additional assistance, to immobilize rabbits safely without the use of drugs or physical restraints while such procedures as heart puncture and intraperitoneal injection are performed.

188. SMITH, O. A., JR. AND DEVITO, J. L. An approach to quantifying various types of spontaneous activity. *Science* 129: 1229–30 (May 1), 1959.

An activity-measuring device for analysis of the behavior of normal animals and animals with surgically produced neural lesions is described. Records are presented for a monkey that was hyperactive after lobectomy and a normal monkey that was engaged in a certain amount of rhythmic behavior. By using a sensitive jiggle cage it might be possible to record and identify also small-amplitude movements such as scratching. It is estimated that the records obtained by this technique account for about 80%–90% of the total energy expended by an animal in somatic muscle activity.

189. STILES, S. W. Induction of ether anesthesia in cats. *Proc. Animal Care Panel* 9: 83–4 (June), 1959.

The cat is placed in a plastic box and an O_2-ether mixture is introduced. Anesthesia is complete in about 9 min. The cat is then removed from the box and anesthesia is continued with an ether cone. The procedure is illustrated in 4 figs.

190. SYKES, J. A. AND MOORE, E. B. A new chamber for tissue culture. *Proc. Soc. Exptl. Biol. Med.* 100: 125–7 (Jan.), 1959.

A simple tissue culture chamber is described which permits phase microscopy at high magnifications and easy staining for permanent record. The chamber is also suited to perfusion studies, permits observation of cells over extended periods, and is useful for time-lapse photography. The chamber has proved valuable in tissue culture studies of material derived from cases of human leukemia, mouse leukemia, mammary carcinoma of mice, and bovine ocular squamous cell carcinoma and its benign precursor lesions. (Author's summary)

191. TEDESCHI, R. E., TEDESCHI, D. H., MUCHA, A., COOK, L., MATTIS, P. A. AND FELLOWS, E. J. Effects of various centrally acting drugs on fighting behavior of mice. *J. Pharmacol. Exptl. Therap.* 125: 28–34 (Jan.), 1959.

Methods to induce changes of behavior patterns (fighting) in some laboratory animals (cat, mouse, rat) are reported.

192. TROWELL, O. A. The culture of mature organs in a synthetic medium. *Exptl. Cell Research* 16: 118–47 (Jan.), 1959.

A culture method is described by which mature organs, or parts thereof, from rats and mice may be maintained *in vitro* in a simple synthetic medium for short-term experiments. The following organs could be kept for 6–9 days: ureter, ductus deferens, uterus, trachea, arteries, salivary glands, mammary gland, prostate, seminal vesicle, lung, thyroid, parathyroid, pituitary, pineal, ovary, skin, white adipose tissue, lymph nodes, sympathetic ganglia. Partial survival was obtained in the case of kidney, adrenal and spinal ganglion. The survival of brain, liver, thymus, spleen, bone marrow, testes and pancreas was unsatisfactory. (Author's summary)

193. U.S. PUBLIC HEALTH SERVICE. Exposure chambers for research in animal inhalation. *Public Health Monograph* No. 57, 1959.

XUM

Design, construction and operating of exposure chambers are discussed. A review of controlled animal inhalation exposure studies is included. (87 references)

THE FOLLOWING ABSTRACTS, although located elsewhere in this bibliography, are related to the subject of this section.

Section 1: 12, 17, 18, 26, 34, 39, 45, 50, 51, 64, 67, 68, 70, 72, 74, 78, 82, 91, 95, 96, 98, 101, 103, 108, 117, 118, 122, 124, 125, 126, 130, 131, 137, 145, 153, 155, 156, 157, 158, 161, 163, 166, 168, 179, 184, 189, 194, 197, 198, 201, 202, 207, 211, 217, 222, 225, 229, 231, 248, 250, 255, 258, 261, 265, 268, 276, 279, 286, 287, 290, 294, 300, 305, 314, 327, 328, 331, 338, 340, 344, 354, 356, 362, 363, 368, 370, 371, 374, 397, 399, 400, 403, 405, 406, 414, 415, 419, 423, 424, 425, 427, 429, 431, 432, 433, 435, 437, 441, 442, 443, 447, 450, 454, 460, 461, 462, 469, 471, 477, 478, 479, 481, 485, 495, 496, 506, 512, 516.

Section 2: 6, 10, 19, 23, 30, 47, 58, 63, 66, 72, 76, 81, 83, 95, 98, 121, 141, 145, 164, 166, 167, 176, 178, 179, 180, 183, 198, 199, 202, 209, 211, 239, 299, 307, 309, 310, 314, 316, 321, 329, 330, 335, 345, 351, 353, 365, 372.

Section 3: 2, 3, 4, 6, 7, 22, 29, 32, 38, 60, 63, 82.

Section 4: 63, 86, 89, 106, 112.

Section 5: 1, 3, 5, 8, 11, 14, 20, 33, 34, 38, 41, 44, 47, 55, 61, 62, 69, 79, 95, 96, 102, 103, 107, 124, 130.

Section 6: 18, 22, 48.

Section 8: 6.

8. Administration of Colonies: Records, Costs, Personnel, Public Relations[1]

1. HENTHORNE, R. D. Rule of thumb methods used by commercial breeders for cost considerations. National Research Council, Institute of Laboratory Animal Resources, mimeo (no date), 2 pp.

Requirements for facilities, number of mice per cage in use and production colony, replacement of production colony, mating system and cost factors are discussed.

2. CUMMING, C. N. W. The importance of the trained animal attendant. *Proc. Animal Care Panel* 1st Ann. Meeting, Nov. 28, 1950, pp. 10–6.

The requirements and duties of a good animal attendant are discussed.

3. SULKIN, S. E. AND PIKE, R. M. Laboratory-acquired infections. *J. Am. Med. Assoc.* 147: 1740–5 (Dec. 29), 1951.

Recent surveys show that laboratory infections can be acquired by professional and technical workers, students, clerical and maintenance workers, and even by visitors to laboratories from all categories of infectious agents—bacteria, viruses, rickettsiae, parasites, and fungi. The resulting illness varies in severity from inapparent infections to those with a fatal outcome. Safety measures instituted by numerous laboratories include various types of ventilating devices, inoculating cabinets, and techniques for the handling of infectious material. In some laboratories available vaccination procedures are in routine use. Laboratory workers should be acquainted with the potential sources of infection and encouraged to make use of available safety measures wherever indicated.

4. MUNDY, A. E. The function of the animal technician. *Lab. Animals Bureau, M. R. C. Lab., Collected Papers* 1: 37–47, 1953.

The responsibilities and duties of animal technicians are outlined. The training programs and aims of the Animal Technician Association are reviewed.

5. FREMMING, B. D., BENSON, R. E., YOUNG, R. J., HARRIS, M. D. AND NACHTWEY, D. S. Record maintenance for a long-term monkey colony. *Am. J. Vet. Research* 16: 470–1 (July), 1955.

A functional and economical system of recording information concerning the health of animals in a monkey colony is described.

6. ANONYMOUS. The Universities Federation for Animal Welfare. *Lancet* 2: 631–3 (Sept.), 1958.

Purpose and goals of the UFAW are explained and its *Handbook on Care and Management of Laboratory Animals* is recommended. The desirability of improving laboratory techniques and methods of handling wild and domestic animals is pointed out.

7. BROOKSBY, J. B. Economics of an animal division: Problems of equating supply and demand. *Lab. Animals Centre, M. R. C. Lab., Collected Papers* 7: 19–29, 1958.

Capital costs of buildings and equipment as well as operating costs of production and experimental units for laboratory animals are discussed. The successful solution of the problem of equating supply and demand contributes essentially to the economic success of an animal division.

8. CHRISTENSEN, L. R. AND COHEN, B. J. Laboratory animal care—a new discipline. *Lab. Animals Centre, M. R. C. Lab., Collected Papers* 7: 63–71, 1958.

A model for the operation of central animal care is presented; functions, administration and economic aspects of central animal care are discussed.

9. ELSDON, S. R., ILLMAN, O. AND SMYTH, D. H. The organization of the field laboratories at Sheffield University. *Lab. Animals Centre, M. R. C. Lab.*, Collected Papers 7: 73–85, 1958.

An account is given of the method of administering the animal house at Sheffield University. Data are given for the number of animals used, bred and sold and the costs for feed.

10. LABORATORY ANIMALS CENTRE, M. R. C. LABORATORIES. *The Organization and Administration of an Animal Division.* (*Collected Papers* vol. 7) Carshalton, Surrey, England, 1958, 107 pp.

The symposium contains an abstract on "The organization and administration of an animal division" by C. HARINGTON; "Economics and efficiency in an animal division" by E. M. KILLICK; "The relation of an animal division to a research division" by S. KOOPMANS; "Scientific research within a laboratory animals division" by C. R. AUSTIN.

For abstracts of other papers, see: Bacharach, A. L., Cuthbertson, W. F. J. and Flynn, G. W.; Brooksby, J. B.; Christensen, L. R. and Cohen, B. J.; Elsden, S. R., Illman, O. and Smyth, D. H.; Flynn, R. J.; Lane-Petter, W. and Lockett, M. F.; Paterson, J. S. and Weitz, B.; Sabourdy, M. A.

11. LANE-PETTER, W. AND LOCKETT, M. F. Animal technician training. *Lab. Animals Centre, M. R. C. Lab., Collected Papers* 7: 101–7, 1958.

Training facilities for animal care technicians are reported.

12. PATERSON, J. S. AND WEITZ, B. G. F. The cost of animals bred and kept for research: A comparison between a large and a small unit. *Lab. Animals Centre, M. R. C. Lab., Collected Papers* 7: 45–55, 1958.

After defining the terms of a large and a small research unit the accounting system for these colonies is discussed. An analysis of total expenditure is shown in a diagram; production and maintenance costs for mouse, rabbit and guinea pig colonies are tabulated. On balance, it appears cheaper to produce animals for local use in small decentralized units than in a few large establishments from which they would be distributed.

[1] Arrangement is chronological by year of publication. A list of additional references, located in other sections of this bibliography, will be found on page 134.

13. PORTER, G. The training of animal technicians in Great Britain. *Proc. Animal Care Panel* 8: 7–12 (Mar.), 1958.

Details of training of animal technicians are described.

14. SABOURDY, M. The staffing of an animal division. *Lab. Animals Centre, M. R. C. Lab., Collected Papers* 7: 93–9, 1958.

Organization and responsibilities of the staff are outlined.

15. PARRISH, H. M., CLACK, F. B., BROBST, D. AND MOCK, J. F. Epidemiology of dog bites. *Public Health Repts.* 74: 891–903 (Oct.), 1959.

Factors associated with dog bites were studied statistically in Pittsburgh, Pa. Tables list the incidence of dog bites, occupations of victims, anatomic location and severity of dog-bite wounds, the victims' accounts of circumstances of dog bite accidents, places, day of week and time of day these occurred, age and sex of licensed dogs inflicting bites and distribution of bites inflicted by various groups of licensed dogs.

16. RUSSELL, W. M. S. AND BURCH, R. L. *The Principles of Humane Experimental Technique.* London, Methuen, 1959, 238 pp.

The book is divided into 2 parts: *1*) the scope, and *2*) the progress of humane technique. Replacement of animals as objects of experiment by insentient material such as tissue cultures, reduction in the numbers of animals used to obtain results of given precision, and refinement of procedures employed when animals still have to be used, are discussed. Legal aspects are briefly discussed, as are the activities of the Laboratory Animals Bureau, Animal Technicians Association and Universities Federation for Animal Welfare.

THE FOLLOWING ABSTRACTS, although located elsewhere in this bibliography, are related to the subject of this section.

Section 2: 82, 122, 124, 217, 223, 323.
Section 3: 6, 24, 88.
Section 4: 10, 13, 26, 39, 49, 50, 59, 65, 66, 68, 76, 83, 109.
Section 5: 19, 21, 25, 30, 32, 43, 74, 87, 89, 90, 101, 102, 110, 115, 123, 125.
Section 6: 12, 26.
Section 7: 92, 99, 172.
Section 9: 14, 20.

9. Periodical and Other Publications of General Interest

1. *American Rabbit Journal.* Warrenton, Missouri, F. H. Hollmann, 1931+.

The journal has been combined with the *Angora Rabbit Magazine* since 1945. It appears monthly and contains original articles and advertisements.

2. *Animal Breeding Abstracts.* Farnham Royal, England, Commonwealth Agricultural Bureaux, 1933+.

This quarterly review of world literature is prepared by the Commonwealth Bureau of Animal Breeding and Genetics, Edinburgh. The subject matter is classified as follows: livestock, general; horse; cattle; sheep; goat; pig; fur bearers; laboratory mammals; other mammals; poultry; other birds; genetics, general; reproduction and sex, general; book reviews and notices.

3. *Bibliography of Agriculture.* U.S. Department of Agriculture Library. Washington, U.S. Government Printing Office, 1942+.

Monthly issues (Jan. to Nov.) listing references only. Detailed author and subject indexes constitute the Dec. issue.

4. *Biological Abstracts.* Philadelphia, Pennsylvania, 1925+.

The world's biological research literature is covered. Sections on animal science and animal production and veterinary science are included.

5. *Bulletin for Medical Research of the National Society for Medical Research.* Chicago, Illinois, 1946+.

Programs, legislation and current events as they apply to acquisition, availability of living and anatomic material for use in biological and medical teaching and research are reported. Humanitarian, ethical and philosophical considerations are included.

6. *Carworth Quarterly Letter,* by E. L. AND C. N. WENTWORTH CUMMING. New City, Rockland County, New York, Carworth Farms, Inc., 1946+.

The letters contain news briefs, notes and comments on recent articles and books as well as original articles dealing with the production, care and use of laboratory animals.

7. *Cats Magazine.* Pittsburgh, Pennsylvania, Cat Fanciers' Association, Inc., 1944+.

A layman's journal including potential sources for the procurement of cats.

8. *Dog Research News.* Los Angeles, California, Albers Milling Company. (No date given)

Dog Research News is published in the interest of the veterinarian to help keep him informed of the latest developments in animal hospital management and the care, feeding and breeding of dogs. Each issue will present original scientific articles.

9. *Dog World.* Chicago, Illinois, Judy Publishing Company, 1916+.

This journal brings short notes concerning care of dogs and contains information on sources of supply.

10. *Gaines Veterinary Symposium: The Newer Knowledge about Dogs.* New York City, Gaines Dog Research Center, 1951+.

A synoptic presentation of papers dealing with the care and health of dogs is published yearly.

11. *ICLA Bulletin,* issued by the International Committee on Laboratory Animals (Secretary-General W. Lane-Petter). London, England, 1957+.

The *Bulletin* appears every March and September. Sources of animals, transportation and international regulations are reported. Included are selected references concerning laboratory animals. The lists of references are published several times per year.

12. *Inbred Strains of Mice.* Bar Harbor, Maine, Roscoe B. Jackson Memorial Laboratory, 1959+.

The 1st issue of this publication appeared in July 1959; additional issues will appear every 2 years. It is an informal mimeographed document which lists laboratories maintaining inbred strains of mice, and is a companion document to *Mouse News Letter* (appearing in England).

13. *Information on Laboratory Animals for Research,* edited by B. Hill. Washington, D.C., National Research Council, Institute of Laboratory Animal Resources, 1958+.

This quarterly bulletin reports on the activity and progress of the organization. It lists its own publications and reports on the national and international picture in laboratory animal organizations, as well as others of particular interest.

14. INTERNATIONAL VETERINARY CONGRESSES, THE SECRETARIAT OF THE PERMANENT COMMITTEE. *List of Veterinary Films and Films of Veterinary Interest.* Utrecht, Netherlands, May 1959, 227 pp.

This catalogue lists films from all the countries of the Permanent Committee as well as from a few countries not represented on this committee. The subject matter is distributed as follows: physiology, protozoan diseases, psychiatry, research, reproduction, rickettsial diseases, surgery, therapeutics, tissue culture, toxicology, viral diseases, zootechny. The addresses of the suppliers are given.

15. *Mouse News Letter,* edited by M. F. Lyon. Carshalton, Surrey, England, Laboratory Animals Centre, 1949+.

This publication appears twice annually. It is an informal mimeographed document carrying information on mutant genes, research stocks of mice, and research news.

16. *The Journal of the Animal Technicians Association.* Carlton, Nottingham, England, Animal Technicians Association, 1950+.

The journal appears quarterly and presents original articles, book reviews, advertisements by British suppliers, etc.

17. Institute of Laboratory Animal Resources, National Research Council. *Continuing Inventory of Non-committed Laboratory Animal Stocks.* Washington, D.C.

A mimeographed list of noncommitted animals, available for immediate delivery, is published every 2 weeks. The listing includes random- and inbred mice, rats, hamsters, guinea pigs and rabbits as well as strain designation of inbred mice. The available number of each group for the Northeast, Southeast, Midwest and West and their weight ranges are shown.

18. *Proceedings of the Animal Care Panel.* Argonne, Illinois, Animal Care Panel, 1950+.

The proceedings were published annually to 1955 and quarterly thereafter. Original work and review papers on production, procurement, care, management and use of laboratory animals are published.

19. *Supply Bulletin.* Bar Harbor, Maine, Roscoe B. Jackson Memorial Laboratory.

The mimeographed bulletin is distributed weekly by the Production Department to keep customers informed on mouse supply at the Laboratory. The available strains, their sex and age are listed.

20. *U.S. Public Health Service Film Catalog.* (*Public Health Ser. Publ.* No. 776) 1960, 66 pp.

Many films on laboratory animals and experimental techniques are included. As new films are produced and released, descriptive announcements are sent to catalog holders on the mailing list.

21. *Veterinary Bulletin.* Farnham Royal, England, Commonwealth Agricultural Bureaux, 1921+.

This monthly abstract journal of world literature is prepared by the Commonwealth Bureau of Animal Health. The references relate mostly to domestic animals, but laboratory animals are also included. Diseases, pharmacology, general therapeutics, physiology, anatomy, biochemistry, reproduction, techniques, apparatus and miscellanea are covered.

Author index

The number of the author entry follows the colon. The italicized number preceding the colon designates the section in which the author entry appears.

Names preceded by *de, von,* etc. are listed under the principal name, e.g. *v. Fellenberg,* unless the prefix is generally accepted (mainly in the United States) as part of the name, e.g. *Von Oettingen.*

Where umlauts occur, the listing assumes the full combinations of *ae, oe,* etc.

Mc and *Mac* are listed together and precede *M* in the alphabetical sequence.

Aboulfia, R., *2:* 50
Abrams, G. E., *1:* 124
Ackerman, C. J., *3:* 41
Adams, A. R., *7:* 168
Adams, C. E., *1:* 395
Adams, C. H., *4:* 118
Adams, D. J., *1:* 338
Adams, S. S., *5:* 93
Adams, W. E., *1:* 322
Adelman, W. J., Jr., *7:* 91
Adlersberg, D., *1:* 412
Adolph, E. F., *1:* 80
Aebi, H., *1:* 221
Afonsky, D., *1:* 198
Agricultural Board, National Research Council, *6:* 17
Ainsworth, G. C., *2:* 291
Ajello, L., *2:* 247, 248, 334
Albers Milling Co., *9:* 8
Albert, S., *1:* 466; *7:* 40
Albrecht, P. G., *7:* 167
Albritton, E. C., *3:* 35
Alexander, B. F., *6:* 34
Alexander, C. S., *1:* 268
Alexander, D. P., *4:* 22
Alg, R. L., *2:* 117
Algeria, *1:* 105
Algire, G. H., *7:* 63
Allen, A. M., *2:* 193
Allen, J. D., *1:* 242
Allen, R., *2:* 187
Allen, R. C., *1:* 323
Allen, S., *3:* 2
Altamero, T. L., Jr., *2:* 107
Altland, P. D., *1:* 420, 421
Ambrus, C. M., *1:* 117; *7:* 32
Ambrus, J. L., *1:* 117; *7:* 30, 32
American Animal Hospital Association, Hospital Building and Equipment Committee, *5:* 25
American Association for the Advancement of Science, Culture Methods for Invertebrate Animals, *4:* 4
Ames, C. T., *7:* 61
Amin, A., *1:* 269
Ancill, R. J., *1:* 187
Andersen, A. C., *1:* 324; *2:* 194; *4:* 100
Anderson, J. T., *1:* 142
Anderson, R. C., *2:* 10; *6:* 11
Andral, L., *2:* 76
Andreotti, H. T., *2:* 311
Andrew, W., *2:* 126
Angeloff, S., *1:* 270
Anghi, C., *1:* 118
Animal Care Panel, *5:* 84, 94; *9:* 18
Animal Care Standards Committee, *6:* 15
Animal Technicians Assoc., *9:* 16
Animal Welfare Institute, *5:* 1, 85; *6:* 35
Annegers, J., *1:* 164
Anonymous, *1:* 325; *2:* 195, 196; *3:* 23, 34, 36; *5:* 35, 48, 105, 126, 127; *6:* 43, 52; *7:* 92, 148, 149; *8:* 6
Anthony, A., *1:* 271
Antliff, H. R., *1:* 272
Apgar, C. S., Jr., *7:* 9
Apter, J. T., *7:* 110
Arabehety, J. T., *7:* 150
Archibald, J., *7:* 172
Archibald, R. T., *7:* 41
Arlein, M. S., *2:* 323
Armed Forces Institute of Pathology, *2:* 197
Armin, J., *7:* 42
Armstrong, W. D., *1:* 230
Arnall, L., *2:* 198
Aronson, A. L., *7:* 151
Asdell, S. A., *1:* 61
Ashley, F. L., *7:* 161
Ashoub, M. R., *1:* 330
Association of American Feed Control Officials, *3:* 37
Atkins, G., *1:* 470
Atkinson, J. D., *2:* 121
Austin, C. R., *1:* 123, 273, 274
Austwick, P. K. C., *2:* 291
Awad, F. I., *2:* 127, 199
Axelrad, A. A., *2:* 240
Axelrod, A. E., *7:* 53
Azarnoff, D. L., *1:* 326

Babineau, L.-M., *1:* 199
Bacharach, A. L., *4:* 83
Bacigalupo, J., *2:* 59
Bacon, B. F., *1:* 342
Baddeley, R. M., *1:* 237
Baer, J. E., *1:* 275
Bailey, C. B., *1:* 276
Baker, A. H., *5:* 86
Baker, B. R., *2:* 211
Baker, G. A., *1:* 52
Baker, J. A., *2:* 33, 128, 230, 292, 293
Baker, J. R., *1:* 10
Baker, N., *2:* 200
Baker, R. D., *7:* 115
Balmain, J. H., *1:* 223
Barclay, W. R., *2:* 315; *7:* 152
Barke, A., *2:* 129
Barnawell, E. B., *5:* 113
Barnes, J. M., *7:* 64
Barnes, M. J., *2:* 332
Barnett, M., *7:* 111
Barnett, S. A., *5:* 106
Barron, C. N., *2:* 294
Barrow, P., *7:* 33
Barrows, C. H., Jr., *1:* 277
Barry, E. D., *4:* 99
Barry, F. S., *7:* 4
Bartlett, R. G., Jr., *1:* 119, 120, 165, 224, 327, 328, 419–422
Bartos, F. J., *4:* 14, 15
Bassett, L., *5:* 16
Bastian, J. W., *1:* 225
Bauer, F. J., *1:* 226
Baumberger, J. P., *3:* 2
Baumgartner, L. L., *5:* 14
Baur, L. S., *3:* 64
Baurmash, L., *7:* 43
Beach, F. A., Jr., *4:* 30; *6:* 7
Beakley, W. R., *1:* 178
Beamer, P. D., *2:* 355
Beatty, R. A., *1:* 227
Becker, E. L., *1:* 166, 228
Becks, H., *1:* 121
Bedford, T., *5:* 60
Beecher, H. K., *1:* 278
Behnke, A. R., *7:* 93
Beidler, L. M., *1:* 200
Beinfield, W. H., *7:* 82
Bell, J. F., *2:* 295
Bell, R. T., *1:* 510
Bellis, D. B., *3:* 42
Benacerraf, B., *1:* 279, 504
Benbrook, E. A., *2:* 75
Benjamin, J. D., *1:* 194
Benjamin, M. M., *2:* 296
Bennett, E. L., *1:* 329
Bennett, H. S., *1:* 423
Bennett, J., *4:* 23
Bensley, B. A., *1:* 81
Benson, R. E., *2:* 158; *5:* 61; *8:* 5
Bering, E. A., Jr., *1:* 424
Berkeley, W. H., *7:* 65
Berman, H. J., *1:* 201
Bernard, J., *1:* 400
Bernard, V. M., *7:* 74
Bernstein, L., *1:* 167, 194; *7:* 94, 121
Bernstein, P., *1:* 327
Berry, G. P., *7:* 11
Berry, R. J., *2:* 232, 233
Best, C., *7:* 66
Bester, J. F., *7:* 36
Bethard, W. F., *2:* 201
Beverley, J. K. A., *2:* 130, 131, 297
Bicks, V. A., *2:* 132
Biester, H. E., *2:* 298; *5:* 49
Biggers, J. D., *1:* 223, 330; *4:* 94
Bild, C. E., *2:* 133, 202; *3:* 75
Bimmer, E., *2:* 203
Binns, W., *7:* 153
Biörck, G., *7:* 72
Biozzi, G., *1:* 279
Birmelin, E. A., *7:* 90
Birren, J. E., *1:* 331, 380
Bishop, E. J., *7:* 44
Bishop, J., *1:* 439
Bishop, M. W. H., *1:* 274
Bissonnette, T. H., *1:* 9, 19
Bittle, J. L., *2:* 348
Bittner, J. J., *1:* 150, 191, 297; *2:* 60, *7:* 167
Bjerkedal, T., *2:* 299
Björck, G., *3:* 43
Black, W. G., *2:* 61
Blackledge, G. T., *1:* 332
Blahd, W. H., *2:* 200
Blair, A. W., *5:* 9
Blair, W. J., *7:* 147
Blakeslee, H. N., *7:* 154
Blandau, R., *1:* 333
Blandin, J., *1:* 335
Blank, F., *2:* 134
Bleicher, N., *7:* 112, 161
Bliss, A. R., *5:* 4, 7
Bliss, G. S., *5:* 4
Bloom, F., *1:* 54, 280
Bloom, J. L., *4:* 73
Blount, W. P., *2:* 135
Blumer, W. F. C., *1:* 425
Boatman, J. B., *1:* 426
Boch, J., *2:* 136
Bock, F., *1:* 149

Bohr, V. C., *1:* 119
Bolam, R., *7:* 66
Bollman, J. L., *7:* 24, 25
Bond, C. F., *1:* 334
Bond, C. R., *4:* 7
Bond, E., *5:* 30, 37
Bongiovanni, A. M., *1:* 58
Borchers, R., *3:* 65
Borda-Bossana, D., *7:* 121
Boréus, L.-O., *7:* 73
Bost, J., *1:* 335
Bothwell, T. H., *1:* 336
Boura, A., *7:* 45
Bourne, G. H., *3:* 44
Boursnell, J. C., *5:* 95
Bowman, E. R., *7:* 171
Boyce, W. H., *7:* 161
Brace, K. C., *1:* 122
Brachet, J., *1:* 427
Braden, A. W. H., *1:* 123, 337
Bradley, O. C., *1:* 428
Brady, J. V., *7:* 155
Braekkan, O. R., *4:* 77
Braithwaite, J. L., *1:* 338
Bramante, P. O., *1:* 429
Brandon, F. B., *2:* 365
Brasseur, L., *1:* 339
Bratton, R. W., *4:* 88
Brewer, J. H., *4:* 13
Brewer, N. R., *1:* 103; *5:* 26, 36, 50, 87; *6:* 59
Briody, B. A., *2:* 300
Briscoe, S., *1:* 168
Brizzee, K. R., *1:* 430
Broadwater, G. C., *2:* 117
Brobst, D., *8:* 15
Brodsky, C., *7:* 93
Brodsky, W. A., *5:* 41
Brody, S., *1:* 306
Brook, G. B., *1:* 20
Brooke, R. O., *5:* 5
Brookreson, A. D., *1:* 431
Brooks, M. B., *5:* 128
Brooksby, J. B., *8:* 7
Brown, D., *3:* 25
Brown, J. H. U., *1:* 251; *7:* 119
Brownell, K. A., *1:* 215
Browning, C. B., *3:* 66
Brozek, J., *7:* 156
Bruce, H. M., *1:* 169; *4:* 3, 11, 12, 31, 43
Bruce, W. R., *7:* 152
Bruckner-Kardoss, E., *1:* 515
Brueckman, C. T., *7:* 114
Bruner, H. D., *1:* 25; *5:* 31
Brunst, V. V., *7:* 46
Bryan, F. A., *7:* 43
Bryant, B. F., *7:* 74
Bube, F. W., *2:* 204
Bucher, K., *2:* 63
Budds, O. C., *1:* 124
Bürki, F., *6:* 14
Büsing, K.-H., *1:* 93
Bunster, E., *7:* 6
Burch, G. R., *7:* 157
Burch, R. L., *8:* 16
Burdon, K. L., *7:* 13
Burgen, A. V. S., *1:* 408
Burgher, J. A., *2:* 230, 293
Burgos, N. H., *1:* 340
Burke, J. D., *1:* 282
Burke, W. C., *7:* 43
Burke, W. T., *1:* 432
Burnet, F. M., *2:* 301
Burns, M., *4:* 24
Burrill, D. Y., *7:* 20
Burstein, S., *1:* 106
Busch, K. A., *2:* 90
Bush, I. E., *1:* 125
Bustad, L. K., *5:* 130
Butterworth, B. B., *1:* 436
Buttle, G. A. H., *7:* 95
Buxton, A., *2:* 137
Byerly, T. C., *4:* 65, 76, 109

Cain, C. B., *7:* 5
Cain, J. C., *7:* 25
Caldwell, J. D., *4:* 118
Calhoun, J. B., *1:* 107
Calhoun, M. L., *1:* 170
California, State of, *6:* 27
Callahan, A. B., *1:* 433
Calvin, L. D., *6:* 18
Cammiade, M. E., *3:* 26
Campbell, D., *5:* 107
Campbell, D. H., *1:* 505
Campbell, H. L., *3:* 12
Campbell, S. L., *3:* 82
Candlin, P. T., *7:* 113
Cannon, M. D., *3:* 8
Cantarow, A., *1:* 262, 351
v. Capeller, D., *2:* 63
Capraro, V., *1:* 126
Carlson, E. R., *7:* 1
Carlson, L. D., *2:* 302
Carmichael, E. B., *5:* 9; *6:* 8; *7:* 3
Carmichael, L. E., *2:* 205
Carnochan, F. G., *2:* 34; *5:* 19
Carpenter, K. J., *1:* 341; *2:* 84
Carpenter, L. E., *4:* 44
Carpenter, P. L., *1:* 229
Carr, M. H., *1:* 434
Carson, J. R., *1:* 342
Case, R. W., *7:* 114
Casey, A. E., *1:* 8
Cass, J. S., *2:* 35; *5:* 108
Cassidy, J., *3:* 45
Castanera, T. J., *1:* 157; *7:* 75
Caster, W. O., *1:* 230
Castor, G. B., *7:* 158
Cat Fanciers' Assoc., *9:* 7
Cathie, I. A. B., *2:* 138
Cavier, R., *2:* 85
Cello, R. M., *2:* 303
Cerisola, H., *2:* 340
Chabaud, M. A., *2:* 76
Chai, C. K., *1:* 269, 283, 343; *2:* 139
Chalberg, C., *6:* 38
Chamberlain, F. W., *1:* 48
Chambers, R. M., *1:* 344
Chance, M. R. A., *6:* 37
Chang, M. C., *1:* 345
Changnon, E., *1:* 11
Chao, F.-C., *1:* 127
Chapman, C. B., *7:* 41
Charles, M. S., *1:* 231
Charles, R. T., *2:* 206; *4:* 59
Charms, B. L., *1:* 435
Chase, H. B., *1:* 137, 171
Cheever, F. S., *2:* 20
Chen, K. K., *1:* 67; *2:* 10; *6:* 11; *7:* 14
Chen, P. S., Jr., *1:* 202
Cheng, C. S., *1:* 306
Cheng, D. W., *2:* 304
Chetrick, A., *1:* 367
Chew, R. M., *1:* 436
Chick, E. W., *7:* 115
Childs, W. A., *1:* 382
Chow, B. F., *1:* 277
Christensen, L. R., *5:* 84; *8:* 8
Christian, J. J., *1:* 128, 203, 204, 287; *2:* 36, 305
Christianson, M., *1:* 284
Church, F., *7:* 28
Church, L. E., *7:* 96
Chute, H. L., *2:* 140, 225
Cizek, L. J., *1:* 172; *3:* 76
Clack, F. B., *8:* 15
Claringbold, P. J., *1:* 223
Clark, B. B., *1:* 51
Clark, C. H., *1:* 437; *2:* 141
Clark, E., *1:* 11
Clark, R. T., Jr., *1:* 206
Clarke, E. G. C., *7:* 97
Clarke, N. P., *7:* 98
Clarkson, T. B., *1:* 285; *2:* 306; *6:* 53; *7:* 116
Clausen, J., *1:* 461
Clayton, R. J., *7:* 46
Clemente, C. D., *4:* 84; *7:* 104
Coffin, D. L., *2:* 47, 142
Cohen, B. J., *2:* 32; *5:* 37, 62; *6:* 38, 63; *8:* 8
Cohen, C., *1:* 129, 205, 232, 346; *7:* 76
Cohrs, P., *2:* 207
Coker, S. T., *7:* 117
Cole, C. R., *2:* 86
Cole, H. H., *1:* 438
Cole, J., *1:* 425
Coleman, N., *2:* 77, 78, 152
Coleman, R. M., *2:* 143
Coleridge, J. C. G., *7:* 47
Coles, B. L., *1:* 286
Collins, K. J., *1:* 298
Columbus, A., *7:* 83
Comar, C. L., *2:* 307; *5:* 79; *7:* 55
Commonwealth Agricultural Bureaux, *9:* 21
Commonwealth Bureau of Animal Breeding and Genetics, *9:* 2
Connell, M. R. E., *2:* 101
Connell, S. J. B., *5:* 3
Conrad, M. C., *1:* 233
Constant, M. A., *2:* 120
Cook, D. L., *6:* 18
Cook, J. E., *2:* 208
Cook, L., *7:* 191
Cook, R., *2:* 48, 87
Cooperman, J. M., *3:* 9
Corbin, J. E., *2:* 144
Corcoran, A. C., *1:* 130
Cornelius, C. E., *1:* 439; *2:* 145, 209
Cornelius, O., *5:* 38
Cossel, L., *2:* 210
Cotchin, E., *2:* 88, 146
Cottam, S. M., *7:* 118
Cottingham, E., *2:* 13
Courtice, F. C., *1:* 49
Covault, C. H., *2:* 308
Cover, M. S., *2:* 147
Cox, D. H., *2:* 211
Cox, G. J., *4:* 38
Cox, H. W., *4:* 33
Cox, W. M., Jr., *1:* 26
Coy, R., *7:* 179
Crabb, E. D., *1:* 62; *2:* 62
Craft, C. E., *7:* 165
Crafts, R. C., *1:* 40
Craig, F. N., *1:* 362
Craig, J. M., *2:* 148
Craigie, E. H., *1:* 94
Crain, R. C., *2:* 212
Cravetz, H., *7:* 30
Crile, G., *1:* 37
Criscuolo, D., *1:* 206, 347, 456; *7:* 91
Croft, P. G., *1:* 207; *7:* 77, 99
Cronheim, G., *2:* 213
Crosby, E. C., *1:* 21
Cross, R. F., *2:* 89
Crouse, C. W., *3:* 62
Crowcroft, P., *1:* 348
Crowley, L. V., *1:* 475
Cueto, C., *7:* 119
Culture Methods for Invertebrate Animals, *4:* 4
Culver, W. E., *1:* 440
Cumming, C. N. W., *2:* 29, 34; *4:* 65, 68; *5:* 19, 63, 109; *6:* 44; *8:* 2; *9:* 6
Cumming, E. L., *9:* 6
Cuozzo, R. F., *5:* 110
Cupps, P. T., *1:* 438
Curry, M. F., *4:* 60
Cuthbertson, W. F. J., *3:* 46
Cutts, J. H., *2:* 350

Damgaard-Nielsen, M., *7:* 72
D'Amour, F. E., *2:* 151
D'Angelo, S. A., *1:* 262, 349
D'Arcy, P. F., *7:* 95
Darmady, E. M., *5:* 111, 112
Davies, M. E., *2:* 149
Davis, D. E., *1:* 287; *2:* 214
Davis, D. H. S., *1:* 350
Davis, D. L., *1:* 441, 442
Davis, E., *2:* 280
Davis, J., *3:* 47; *5:* 88
Davis, J. E., *1:* 50
Davis, R. F., *3:* 31
Davis, R. K., *2:* 90
Davis, T. R. A., *1:* 173
Dawes, G. S., *1:* 443
Dawson, H. A., *2:* 288
Dawson, R. L., *1:* 477
Day, P. L., *1:* 32
Dearstyne, R. S., *1:* 17
Deavers, S., *1:* 374; *2:* 314
DeBias, D. A., *1:* 351
Degelman, J., *1:* 433
de Graaf, W., *7:* 124
de Grouchy, J., *1:* 400
Deichmann, W. B., *2:* 336; *7:* 23
Delay, J., *7:* 48
Del Greco, F., *1:* 130
DeLuca, H. A., *7:* 86
Denenberg, V. H., *1:* 352, 444

Deniz, N., *7:* 67
Denton, A. E., *1:* 131
Denz, F. A., *7:* 64
DeOme, K. B., *5:* 113
DePugh, R. B., *1:* 234
Deringer, M. K., *2:* 49; *4:* 101
Derivaux, J., *1:* 353
Derum, J. W., *4:* 49
Desclin, L., *1:* 132
De Somer, P., *2:* 153
Deterling, R. A., Jr., *7:* 22
Dethier, B. G., *3:* 77
Dettli, L., *2:* 63
Dettmers, A., *4:* 61
Detrick, L. E., *7:* 37
Detweiler, D. K., *2:* 150, 215
Devine, J. J., *2:* 323
DeVito, J. L., *7:* 188
Dewar, A. D., *1:* 288, 289
Dews, P. B., *7:* 49
Diamant, E., *7:* 121
Dick, G. W. A., *2:* 91
Dicker, S. E., *7:* 45
Dickie, M. M., *1:* 208
Dickinson, R. W., *7:* 43, 45
Dickman, S. R., *5:* 51
Dickson, A. D., *2:* 179
Dickson, W. M., *2:* 313
Didisheim, P., *1:* 445
Dierker, M., *7:* 23
Diesem, C. D., *1:* 354
Dieterich, W. H., *5:* 52
Dietz, A. A., *1:* 63
Dikshit, P. K., *1:* 235; *2:* 216
District of Columbia, *6:* 45
Dittmer, D. S., *1:* 394, 486; *2:* 347
Dobberstein, J., *1:* 355; *7:* 100
Dobson, H. L., *1:* 242
Dodge, C. H., *1:* 292
Doggart, J. R., *1:* 356
Doggett, V. C., *1:* 236
Dohan, J. S., *6:* 9
Dolan, M. M., *2:* 217, 309
Dolcini, H., *7:* 150
Dolowy, W. C., *2:* 310; *7:* 120, 159
Domenico, A. D., *2:* 311
Donaldson, H. H., *1:* 2, 7
Donati, E. J., *4:* 72
Donnelly, G. L., *7:* 18
Dougherty, T. F., *1:* 133
Doughty, M. F., *2:* 293
Dow, C., *2:* 312
Dowben, R. M., *2:* 174
Dowling, M. T., *3:* 27
Downie, H. G., *7:* 172
Downing, T. O., *4:* 72
Draper, H. H., *7:* 84
Dreyfus, J. C., *1:* 400
Drummond, R. O., *6:* 46
Dubos, R. J., *2:* 218
Dubreuil, R., *1:* 134
Duhring, F. L., *4:* 2
Dukes, H. H., *1:* 27
Dumas, J., *1:* 135
Dunbar, E., *7:* 89
Dunlap, J. S., *1:* 218; *2:* 313
Dunn, T. B., *1:* 174; *2:* 49
Dunne, H. W., *2:* 219
Dupont, J. R., *2:* 314
Dupuis, Y., *3:* 48
Dyce, K. M., *7:* 85, 101
Dye, N., *1:* 329
Dyrendahl, S., *3:* 43

Easterday, O. D., *5:* 114
Eaton, O. N., *2:* 37; *4:* 34; *6:* 19
Eayrs, J. T., *1:* 237, 175; *7:* 68
Ebnöter, P., *1:* 221
Eddie, B., *2:* 43
Eddy, H. A., *3:* 86
Ederstrom, H. E., *1:* 82
Edwards, C. H., *7:* 160
Edwards, G. A., *7:* 160
Edwards, J. W., *7:* 161
Edwards, R. G., *1:* 293; *4:* 48
Eggleton, M. G., *1:* 95, 136
Eichwald, E. J., *7:* 78
Eisen, A. Z., *1:* 137
Eisen, L., *7:* 162
Eitzman, D. V., *1:* 446
Elcoate, P. V., *2:* 252
El Hindawy, M. R., *1:* 77
Elias, C., *4:* 68
Elkinton, J. R., *1:* 464
Ellinger, F., *3:* 38
Elliott, R. F., *3:* 49
Elrick, H., *7:* 94, 121
Elsdon, S. R., *8:* 9
Elvehjem, C. A., *1:* 131; *3:* 8, 9
Emmens, C. W., *4:* 11
Emmons, C. W., *2:* 220
Enders, J. F., *2:* 21
Endicott, K. M., *1:* 55; *4:* 65
Endo, M., *2:* 170
England, D. C., *4:* 35, 44
Engle, C., *2:* 328
Engle, M., *1:* 435
Ensminger, M. E., *3:* 52
Enticknap, J. B., *2:* 92, 93
Epstein, F. H., *1:* 373
Epstein, L. I., *1:* 426
Epstein, S. S., *7:* 122, 123
Erickson, B. R., *2:* 151
Ershoff, B. H., *1:* 138
Erve, P., *1:* 517
Essex, H. E., *7:* 22
Evans, C. A., *2:* 56
Evans, F. L., *1:* 139; *5:* 11
Evans, H. M., *1:* 121
Evans, J., *7:* 115
Evans, S., *6:* 21
Everett, N. B., *1:* 108, 447
Everitt, A. V., *1:* 357, 358, 359; *3:* 67
Everson, G. J., *1:* 462, 463
Exley, S. H., *3:* 68
Eyles, D. E., *2:* 77, 78, 152
Eyquem, A., *1:* 176
Eyssen, H., *2:* 153

Fahlberg, W. J., *1:* 242
Fainstat, T. D., *4:* 17
Falconer, D. S., *4:* 25
Fand, I., *1:* 290
Fankhauser, R., *2:* 94
Fantes, K. H., *2:* 322
Fantl, P., *1:* 291
Farber, E., *2:* 271
Farber, J. F., *4:* 72
Farber, S., *5:* 19
Farhi, A., *2:* 154
Farhi, L., *7:* 102
Farid, Z., *2:* 315; *7:* 152
Farner, D. S., *1:* 140
Farrand, R. L., *1:* 238; *3:* 50
Farrell, G. L., *1:* 141
Farris, E. J., *1:* 45, 83; *5:* 19, 27
Favour, C. B., *1:* 53
Feenstra, E. S., *4:* 87
Feist, J. H., *7:* 29
Fekete, E., *1:* 177
Feldman, W. H., *2:* 155
Fellows, E. J., *7:* 191
Fendrick, A. J., *2:* 309; *5:* 89
Fenton, P. F., *3:* 27
Ferguson, I. D., *3:* 25; *5:* 53; *7:* 50
Ferguson, W. S., *3:* 28
Ferreira-Neto, J. M., *2:* 316
Ferrini, O., *1:* 109
Fidanza, F., *1:* 142
Field, E. J., *7:* 103
Field, L. W., *7:* 124
Filer, L. J., Jr., *3:* 64
Finch, C. A., *1:* 336
Findlay, J. D., *1:* 178
Finkler, A. E., *1:* 413
Fischer, K. C., *7:* 61
Fischer, M. I., *2:* 252
Fischer, R. G., *5:* 20
Fischer, W., *2:* 221
Fisher, A. E., *1:* 318
Fisher, L. E., *2:* 30
Fishler, J. J., *2:* 317
Fishman, I. Y., *1:* 200
Fiske, V. M., *1:* 41
Fitzhugh, O. G., *5:* 66
Flamm, H., *2:* 156
Fleisch, A., *7:* 19
Fleischner, J. R., *1:* 448
Flint, J. C., *2:* 222
Flores, V., *2:* 107
Flynn, R. J., *2:* 64, 79, 318, 319, 320; *5:* 30, 39, 54, 84, 90, 115; *7:* 60
Foerster, G. E., *1:* 456
Folger, G. C., *2:* 89
Folk, G. E., Jr., *1:* 238, 292, 317, 360, 361, 398; *3:* 50; *5:* 116; *7:* 142
Folk, M. A., *1:* 292
Follett, A. T., *5:* 40
Fontaine, M., *2:* 157
Fontanares, P. E., *3:* 87
Foote, R. H., *4:* 88
Forbes, M., *1:* 499; *3:* 78
Foster, G. L., *1:* 327
Foster, H. L., *2:* 223, 224; *4:* 85, 102; *5:* 129
Fountaine, F. C., *3:* 66
Fowler, R. E., *1:* 293
Fox, H., *2:* 2
Francis, L. D., *1:* 28
Frank, J. A., *1:* 133
Franke, K. W., *5:* 10
Franke, W. R., *5:* 10
Frankel, H., *1:* 502
Frankel, H. M., *1:* 361, 362, 449
Fraser, A. S., *1:* 193
Fraser, R., *7:* 41
Fratta, I., *6:* 41
Frazer, J. F. D., *1:* 209; *4:* 22, 62
Frazer, S. C., *7:* 125
Fredrickson, T. N., *2:* 225; *7:* 126
Freedman, D. G., *1:* 363
Freeman, W. J., *7:* 163
Fremming, B. D., *2:* 158; *5:* 61, 104; *8:* 5
Frenkel, J. K., *2:* 159
Freund, M., *4:* 86
Frick, E. J., *2:* 22
Fried, G. H., *1:* 143
Friedman, C. L., *1:* 364
Friedman, J. J., *1:* 210, 450
Friedman, S. M., *1:* 70, 364
Frimmer, M., *6:* 22
Frings, H., *4:* 36
Frings, M., *4:* 36
Fritzsche, K., *2:* 226
Froman, R. O., *1:* 474
Frommer, G. P., *1:* 352
Frost, R. C., *2:* 95
Fry, B. A., *2:* 131
Fuentes, C. A., *2:* 50
Fuerst, H. T., *2:* 189
Fuhrman, G. J., *1:* 64
Fuller, C. A., *1:* 410; *4:* 103
Fuller, J. L., *1:* 96, 129, 144, 179, 231; *2:* 96; *6:* 28
Fulton, G. P., *1:* 201, 163; *6:* 29
Fuson, R. B., *7:* 78

Gabka, J., *2:* 160
Gabourel, J. D., *1:* 211
Gaddum, J. H., *7:* 15, 164
Gadsden, E. L., *7:* 160
Gaebler, O. H., *7:* 7
Gafford, R. D., *7:* 165
Gaines Dog Research Center, *9:* 10
Gaines, J. G., *1:* 138
Galaboff, S., *1:* 270
Gale, D., *7:* 166
Gale, L. C., *4:* 10
Gallagher, D. J. A., *1:* 145
Galtsoff, P. S., *4:* 4
Gambaro, C. G., *1:* 109
Gambles, R. M., *2:* 38
Gammage, L., *3:* 88
Gandal, C. P., *2:* 321
Gans, J. H., *7:* 151
Garcia, J. F., *1:* 294
García Rodríguez, I., *2:* 161
Gardner, G. D., Jr., *5:* 101
Gardner, M. V., *1:* 71
Garner, R. J., *2:* 162
Gaspar, S. N., *1:* 239
Gates, A. H., *1:* 295
Gatz, A. J., *1:* 97
Gault, M., *1:* 250
Gay, W. I., *5:* 96; *6:* 54
Gee, W., *1:* 324
Geiger, E., *1:* 240, 365
Geiger, J. F., *1:* 463
Gentles, J. C., *2:* 227, 322
Gentry, R. F., *2:* 228
Gentzkow, C. J., *7:* 81
Georg, L. K., *2:* 163
George, L. A., *5:* 130
George, W., *1:* 146
Gerald, P. S., *1:* 401
Gershoff, S. N., *1:* 31; *3:* 39, 79

Ghadially, F. N., *1:* 366
Ghanem, Y. S., *1:* 261
Ghosh, M. N., *7:* 79
Gierschik, H., *2:* 129
Gilbert, C., *2:* 229
Gillespie, J. H., *2:* 230, 293
Gillman, J., *2:* 229
Gillman, T., *1:* 98
Gilman, B., *2:* 230
Ginsburg, B. E., *1:* 179
Glaja, A., *3:* 21
Gledhill, A. W., *2:* 39, 80, 91, 164
Gleeson-White, M. H., *5:* 95
Gleiser, C. A., *2:* 68
Gletfelty, D. R., *4:* 96
Glimstedt, G., *6:* 55
Gochenour, W. S., Jr., *6:* 24
Goetzl, F. R., *7:* 20
Goff, L. G., *1:* 79
Goffe, A., *2:* 97
Goldberg, H. C., *2:* 323
Goldhaber, P., *2:* 369
Goldie, H., *1:* 180
Goldstein, J., *2:* 98
Goldwasser, R., *7:* 51
Goldzveig, S. A., *1:* 241
Goodale, W. T., *7:* 52
Goodyer, A. V. N., *1:* 367
Gorczyca, L. R., *1:* 451
Gordon, A. S., *1:* 290
Gordon, H. A., *1:* 452; *4:* 111
Gordon, J. E., *2:* 361
Gordon, R. F., *2:* 99
Gorrill, R. H., *2:* 100
Gosselin, R. E., *1:* 211
Goto, G., *2:* 272
Gottlieb, P. M., *2:* 19
Gourley, D. R. H., *1:* 161
Gourzis, J. T., *2:* 213
Govier, W. M., *7:* 89
Gowen, J. W., *6:* 23, 30
Goy, R. W., *1:* 296, 301
Grad, B., *1:* 147
Graham, J. B., *1:* 465
Graham, R., *2:* 11
Graham, R. G., *1:* 242
Graham, R. M., *1:* 465
Graham, W. R., *4:* 87
Grande, F., *1:* 191
Grant, R. T., *7:* 8, 42
Grauwiler, J., *1:* 368
Graves, A. P., *1:* 56
Graves, J., *1:* 212
Gray, A. T., *7:* 50
Gray, D. E., *7:* 86
Gray, E. H., *2:* 51
Gray, E. LeB., *4:* 49
Gray, R. S., *7:* 53
Gray, S. J., *7:* 150
Grazer, F. M., *7:* 104, 127
Great Britain
  Committee of the Privy Council for Agricultural Research, *1:* 369
  Home Office, *6:* 47
  Ministry of Health, *3:* 80
Grebe, R. M., *1:* 394, 486; *2:* 347
Green, E. L., *1:* 148
Green, M. F., *1:* 11
Greene, E. C., *1:* 453
Greene, R. L., *5:* 15
Greenman, M. J., *4:* 2
Greenwald, G. S., *1:* 243
Greganti, F. P., *7:* 87
Gregersen, M. I., *1:* 34; *7:* 67
Gregoire, A. T., *4:* 88
Gregory, E. R. W., *2:* 101
Grice, H. C., *2:* 101
Griesemer, R. A., *2:* 231
Griffin, C. A., *2:* 40, 41; *3:* 51
Griffith, D. R., *1:* 454
Griffith, J. Q., Jr., *1:* 45
Grimes, E. F., *2:* 280
Grimwood, L. H., *1:* 145
Grindeland, R. E., *1:* 360
Grindley, J. H., *7:* 25
Grishman, E., *1:* 501
Grist, N. R., *5:* 64
Gross, L., *5:* 3
Gross, P., *2:* 324; *7:* 128
Grosvenor, C. E., *1:* 244
Grove, A. J., *1:* 266
Gruchmann, W., *1:* 93
Grüneberg, H., *1:* 110, 181, 213, 245
Grunsell, C. S., *4:* 50
Grunt, J. A., *2:* 232, 233
Grunzke, M. E., *7:* 177
Guenther, F., *2:* 102
Guerin, M., *2:* 65
Guerrant, N. B., *3:* 69
Guest, G. M., *5:* 41; *7:* 129
Gunkel, R. D., *7:* 174
Gustafsson, B. E., *1:* 370; *4:* 104
Gutekunst, R. R., *2:* 234
Guttentag, O. E., *7:* 93
Guyton, A. C., *1:* 72, 478; *7:* 87
Guzman, M. A., *1:* 195

Habermann, R. T., *2:* 31, 66, 165, 166, 190, 235, 236, 277, 325
Hackel, D. B., *7:* 52
Hackl, H., *7:* 69
Hadek, R., *4:* 89
Hadgraft, J. W., *7:* 70
Haeger, K., *7:* 72
Haenel, H., *1:* 246
Hafez, E. S. E., *1:* 455
Hagen, K. W., Jr., *2:* 237, 326
Hagquist, C. W., *1:* 29
Hajsig, M., *2:* 103
Halberg, F., *1:* 149, 150, 182, 183, 297, *7:* 167
Hale, C. W., *1:* 57
Hale, H. B., *1:* 385, 386, 387, 456
Haley, A. J., *2:* 238
Haley, T. J., *7:* 54
Hall, C. E., *7:* 168
Hall, F. G., *1:* 495
Hall, O., *7:* 168
Hall, R. A. *4:* 16
Hallanger L. E. *2:* 104
Halliday, R., *7:* 118
Halloran, P. O., *2:* 81
Hallpike, C. S., *7:* 66
Halpern, B. N., *1:* 279
Ham, W. E., *3:* 52
Hamerston, O., *1:* 297
Hamilton, J. B., *1:* 99
Hamilton, J. W., *3:* 5, 11
Hamilton, L. H., *1:* 184
Hamilton, W. F., *1:* 441, 442
Hammond, J., *1:* 4, 185, 457
Hampton, J. C., *1:* 423
Hanel, E., Jr., *5:* 92
Hankin, L., *4:* 90
Hanna, C. H., *1:* 214, 255
Hannah, J. R., *1:* 67
Hannon, J. P., *1:* 458
Hansard, S. L., *5:* 55; *7:* 31, 55
Hansens, E. J., *2:* 105
Hansson, C.-H., *7:* 130, 131, 132
Hardiman, C. W., *1:* 200
Harding, H. B., *2:* 32
Hardwick, D. C., *1:* 186
Hardy, A. B., *2:* 67
Hare, W. C. D., *1:* 459; *2:* 239
Hargreaves, C. C., *5:* 32
Harper, A. E., *3:* 70
Harrington, J. D., *1:* 460
Harris, C., *1:* 432
Harris, M. D., *2:* 158; *5:* 104; *8:* 5
Harris, N. O., *7:* 133
Harris, R. S., *1:* 187; *6:* 56
Harrison, B. M., *1:* 247
Harrisson, J. W. E., *1:* 117; *7:* 30, 32
Harrop, A. E., *4:* 63
Hart, E. B., *3:* 8
Hart, R. J. C., *4:* 69
Hartley, J. L., *7:* 133
Hartman, C. G., *1:* 13, 111; *4:* 8
Hartman, F. A., *1:* 215, 496
Harvey, D. G., *1:* 371; *7:* 105
Hattori, K., *1:* 445
Hausberger, B. C., *1:* 372
Hausberger, F. X., *1:* 372
Hawkins, A. E., *7:* 97
Hazleton, L. W., *1:* 219
Heath, J. P., *1:* 46
Hediger, H., *1:* 85
Hegsted, D. M., *3:* 39
Heidelberger, C., *5:* 33
Heim, G., *5:* 81
Heinemann, W. W., *3:* 52
Hellmann, K., *1:* 298
Helmendach, R. H., *1:* 119
Hemmings, W. A., *5:* 65
Henderson, F. G., *6:* 11
Hendricks, W. A., *3:* 32
Hendrikx, A., *1:* 373
Henry, K. M., *5:* 42
Henschel, J., *1:* 188
Henthorne, R. D., *4:* 70, 105; *8:* 1
Herdan, G., *1:* 187
Heremans, J., *1:* 461
Heremans, M. Th., *1:* 461
Herman, C. M., *2:* 9
Herman, J. A., *1:* 299
Herndon, J. F., *3:* 53
Heron, W., *1:* 196
Heroux, O., *1:* 300
Herrera Repullo, A., *2:* 161
Herrick, C. J., *1:* 3
Herrick, J. F., *2:* 155
Herrlein, H. G., *2:* 327; *4:* 45; *5:* 28, 117
Herrmann, E. C., Jr., *2:* 328
Herrmann, R. G., *1:* 474
Hess, A., *1:* 216
Hess, S. M., *5:* 66
Hesse, A. L., *7:* 120, 159
Heston, W. E., *1:* 151, *2:* 49
Hewitt, H. B., *2:* 167
Heywang, B. W., *3:* 58
Higgins, C. T., *1:* 104
Higgins, W. H., *1:* 411
Hilgar, A. G., *1:* 484
Hill, B. F., *6:* 63; *9:* 13
Hill, J. W., *5:* 23
Hill, R., *1:* 225
Himwich, H. E., *1:* 212
Hindle, E., *4:* 3
Hines, H. M., *1:* 248, 250
Hint, H. C., *7:* 134
Hirsch, S., *2:* 106; *7:* 135
Hitchings, G. H., *2:* 159
Hoag, W. G., *6:* 24
Hoar, R. M., *1:* 296, 301, 302
Hoerlein, B. F., *2:* 329
Hoet, P. L., *1:* 152
Hogan, A. G., *3:* 5, 11
Holbrook, A. A., *2:* 331
Horger, L. M., *1:* 303
Horn, K. H., *3:* 81
Horn, V., *1:* 153
Horowitz, R. E. *1:* 475
Horsburgh, D. B., *1:* 46
Horstman, V. G., *5:* 130
Hort, W., *1:* 100
Horton, R. E., *1:* 499
Horváth, G., *4:* 71
Horvath, M., *7:* 88
Horvath, S. M., *1:* 154, 184; *7:* 169
Horváth, Z., *2:* 52
Horwitz, S. A., *1:* 155
Hoskins, H. P., *2:* 178, 330
Houchin, O. B., *1:* 97
Houglum, M. W., *1:* 183
Hove, E. L., *3:* 53
Howard, E. M., *7:* 95
Howell, C. D., *7:* 169
Hoyland, F., *5:* 97
Hrdina, L. S., *7:* 2
Hrubant, H. E., *1:* 304
Hubbard, E. D., *2:* 374
Huber, G. C., *1:* 21
Huddleson, I. F., *7:* 1
Hudman, D. B., *4:* 118
Hudson, G., *1:* 305
Hudson, R. G., *5:* 98
Huggins, R. A., *1:* 374; *2:* 314
Hughes, J. P., *1:* 500
Hughes, K. E. A., *5:* 111, 112
Hughes, R., *1:* 249
Hull, T. G., *2:* 82
Human, L. E., *1:* 365
Hume, E. M., *2:* 168
Hummel, K. P., *1:* 375; *2:* 357
Hundemann, A. S., *2:* 331
Hunt, H. R., *2:* 288
Huppert, M., *2:* 335
Hurley, L. S., *1:* 462, 463
Huth, E. J., *1:* 464
Hutt, B. K., *1:* 154

Hutt, F. B., *4:* 9; *5:* 19; *6:* 3
Hyman, C., *7:* 56

Iacovino, A., *1:* 517
Iglesias, R., *1:* 376; *2:* 340
Illman, O., *8:* 9
Imaizumi, K., *2:* 170
Imig, C. J., *1:* 248, 250
Ingle, D. J., *1:* 217; *2:* 107, 370
Innes, J. R. M., *2:* 108, 109, 169; *4:* 72
Institute of Laboratory Animal Resources, *4:* 65; *6:* 58; *9:* 13
International Veterinary Congresses, Secretariat of the Permanent Committee, *9:* 14
Irving, S. D., *1:* 140
Irwin, S., *7:* 89
Isaac-Mathy, M., *1:* 339
Isaacson, J. H., *5:* 43
Isler, H., *2:* 240
Isojima, S., *1:* 465
Ito, S., *2:* 170
Ives, M., *7:* 154
Ivy, A. C., *7:* 4, 20
Iyer, P. R. K., *2:* 110

Jack, A., *7:* 166
Jackson, B. J., *2:* 302
Jacobs, B. B., *1:* 377
Jacobs, J., *1:* 251
Jacobs, L., *2:* 171
Jaffe, R., *2:* 207
Jahn, U., *1:* 153
Jakway, J. S., *2:* 241
James, L. F., *7:* 153
Janků, I., *2:* 275
Jaques, L. B., *1:* 314
Jarrett, W. F. H., *2:* 312
Jay, G. E., Jr., *1:* 151; *4:* 37
Jenkins, D. W., *2:* 53; *6:* 39
Jennings, F. W., *2:* 312
Jennings, H. S., *1:* 18
Jensen, L., *1:* 333
Jensen, R., *2:* 222
Joffe, M. H., *1:* 189
Johannisson, D., *7:* 131
Johansen, E., *1:* 156; *7:* 38
John, R., *7:* 16
Johnson, B. C., *3:* 72
Johnson, E., *1:* 378
Johnson, H. D., *1:* 306, 307, 379
Johnson, H. H., Jr., *1:* 252
Johnson, L., *3:* 82
Johnson, R. M., *1:* 466; *7:* 40
Johnson, T. N., *1:* 308
Johnson, V. L., *1:* 218; *2:* 313
Johnston, C. D., *1:* 219
Jones, A. M., *1:* 180
Jones, D. C., *1:* 157
Jones, I. C., *1:* 284
Jones, J. D., *5:* 111, 112
Jones, L. M., *2:* 172
Jones, L. P., *2:* 332
Jones, M. F., *2:* 349
Jones, R. O., *1:* 338
Jones, T. C., *2:* 68, 185
Jones, W. M., *6:* 48
Jordon, P. H., *7:* 106
Joseph, B. J., *1:* 166, 228
Joslin, D., *7:* 39
Joysey, V. C., *1:* 467
Junnila, W. A., *1:* 342
Just, T., *1:* 468

Kagan, J., *4:* 30
Kalm, M. A., *6:* 18
Kalser, S. C., *1:* 211
Kampschmidt, R. F., *2:* 333
Kao, K.-Y. T., *1:* 469
Kaplan, H. M., *2:* 173, 242; *5:* 56, 99
Kaplan, M., *3:* 82
Kaplan, M. M., *2:* 262
Kaplan, S., *2:* 323
Kaplan, W., *2:* 163, 247, 334
Kappers, C. U. A., *1:* 21
Karlson, A. G., *2:* 155
Karlsson, H., *1:* 329
Kartman, L., *2:* 24
Kassel, R., *7:* 57
Kaunitz, H., *1:* 151
Kay, H., *1:* 331, 380
Kedder, H. E., *2:* 61
Keeler, C. E., *7:* 17
Keeney, E. L., *2:* 335
Keil, H. L., *2:* 3
Keller, D. L., *1:* 253
Kellett, D. N., *7:* 95
Kelley, G. W., *4:* 118
Kellogg, C. E., *3:* 15
Kelly, J. W., *1:* 17
Kelsall, M. A., *2:* 62
Kemmerer, A. R., *3:* 58
Kennedy, G. C., *1:* 381
Kent, G. C., Jr., *1:* 470
Kent, S. P., *2:* 174, 243
Keplinger, M. L., *2:* 336
Kerkmann, O. H., *5:* 67
Kerr, M. E., *5:* 130
Kester, W. O., *4:* 105
Keys, A., *1:* 142
Kibrick, A. C., *1:* 471
Kidwell, J. F., *4:* 91
Kimeldorf, D. J., *1:* 157
Kincaid, J. F., *7:* 90
King, D., *1:* 318
King, H. D., *1:* 7, 35
King, J. S., Jr., *1:* 285; *7:* 116
Kinkel, M. P., *5:* 80
Kinsel, G. V., *5:* 118
Kirk, H., *2:* 54, 69
Kirk, R. W., *4:* 106
Kitts, W. D., *1:* 276
Kitzmiller, K. V., *7:* 23
Klecak, G., *3:* 84
Kleiber, M., *1:* 52
Kligman, A. M., *2:* 217
Kniazuk, M., *7:* 10, 80, 136
Knill, L. M., *1:* 382
Knisely, W. H., *2:* 232, 233
Knodt, C. B., *5:* 119
Knox, W. E., *1:* 476
Kobylinski, P. G., *2:* 217
Koch, T., *1:* 355
Koch, W., *5:* 81
Kolmer, J. S., *1:* 101
Kooch, W., *7:* 90
Koprowski, H., *2:* 86
Koyama, R., *2:* 170
Krech, D., *1:* 329
Kreier, J. P., *2:* 355
Kreshover, S. J., *2:* 337
Krise, G. M., *1:* 383; *2:* 175, 338
Krough, A., *1:* 42
Krutzsch, P. H., *2:* 187
Kühl, I., *2:* 221
Kuleshova, V. G., *4:* 92
Kullander, S., *2:* 339
Kunde, M. M., *1:* 11

Laboratory Animal Breeders Association, *6:* 57
Laboratory Animals Bureau, M.R.C. Laboratories, *2:* 111; *3:* 54; *4:* 51; *5:* 68; *7:* 107
Laboratory Animals Centre, M.R.C. Laboratories, *8:* 10
Lacefield, D. J., *1:* 473
Lack, C. H., *5:* 120
Lacroix, J. V., *2:* 178, 330
Laidlaw, P., *4:* 5
Lainson, R., *2:* 176
Lamotte, J., *4:* 98
Lamus, B., *1:* 141
Landry, S. O., Jr., *1:* 472
Lane-Petter, W., *3:* 26, 55; *4:* 73; *5:* 102; *6:* 25, 26, 40; *8:* 11; *9:* 11
Lang, S., *1:* 486
Langston, W. C., *1:* 32
Lanier, G. E., *2:* 336
Lapage, G., *2:* 112
Larsen, E. G., *1:* 473
Last, J. H., *7:* 27
Lategola, M. T., *1:* 309
Latimer, H. B., *1:* 86, 102, 310
Laug, E. P., *5:* 66; *7:* 21
Laurell, C. B., *1:* 370
Lazarow, A., *5:* 69
Leach, L. J., *7:* 137
Leach, W. J., *1:* 112
Leader, V. R., *3:* 29
Leahy, J. R., *7:* 33
Leblond, C. P., *1:* 402; *2:* 240
Lebo, D., *1:* 158
Lee, C.-C., *1:* 474
Lee, H. W.-T., *1:* 483; *2:* 244
Lehr, D., *7:* 82
Lentini, E., *3:* 39
Lentz, W. J., *1:* 22
Leonard, C. A., *7:* 30
Lester, D., *2:* 12
Lev, M., *3:* 78
Levenson, S. M., *1:* 475
Levi, W. M., *1:* 311
Levin, L., *3:* 6
Levine, N. D., *2:* 11, 177
Levitan, S., *7:* 57
Lewis, H. E., *3:* 56
Lewis, J. H., *1:* 445
Lewis, L. A., *1:* 65
Lewis, R. C., *5:* 6
Liljegren, E. J., *1:* 84
Limon, J. M., *1:* 451
Lin, E. C. C., *1:* 476
Linden, R. J., *7:* 47
Linder, M. J., *7:* 58
Lindsay, H. A., *1:* 477
Lindsey, A. W., *1:* 478
Lindt, C. C., *7:* 61
Lindt, S., *2:* 245
Ling, H. W., *7:* 108
Lints, H. A., *1:* 103
Lipschutz, A., *2:* 340
Little, A. D., Inc., *5:* 21
Littlewood, G., *7:* 59
Liu, T. Y., *1:* 215
Liuzzo, J. A., *7:* 138
Llaurado, J. G., *7:* 139
Lloyd, R. G., *3:* 51
Lobl, K., *1:* 491
Lockett, M. F., *8:* 11
Loeffel, W. J., *6:* 17
Lofland, H. B., *2:* 306
Lojda, A., *2:* 275
Lombard, L. S., *2:* 341
Lonsdale, F., *2:* 246
Loosli, J. K., *3:* 13, 31, 40; *5:* 19
Lord, C. F., Jr., *7:* 114
Loustalot, P., *2:* 229
Lucas, C. C., *2:* 191
Luckey, T. D., *3:* 83
Luft, J., *1:* 423
Lumb, W. V., *2:* 296, 342; *7:* 170
Lund, E. E., *4:* 18
Lundberg, W. O., *4:* 74
Lunde, M. N., *2:* 171
Lutz, B. R., *1:* 201, 433
Lutz, F. E., *4:* 4
Lutz, W., *2:* 229
Lyon, M. F., *4:* 64; *9:* 15

McAlpine, U. L., *6:* 2
McArthur, W., *1:* 479
MacCarthy, A., *6:* 36
McCarty, R. T., *1:* 451
McCay, C. M., *3:* 16, 51; *6:* 1
McClendon, J. F., *6:* 4
McClure, T. J., *1:* 384
McCormick, J. A., *7:* 140
McCoy, T. A., *2:* 333
McCrady, E., *1:* 30
McCredie, J. A., *1:* 356
McDiarmid, A., *6:* 16
Macdonald, I., *4:* 93
McFarland, S., *2:* 303
MacFarlane, W. V., *1:* 312
McGavack, T. H., *1:* 469
McGilvray, W., *7:* 28
McGrath, J. T., *2:* 113
McIntyre, W. I. M., *2:* 312
McKeever, S., *2:* 247, 248
McKennis, H., Jr., *7:* 171
McKennis, Q. S., *7:* 171
McKinney, S. E., *1:* 275
McLaren, A., *1:* 190, 330; *4:* 94
McLean, D. L., *2:* 186
McLin, E. D., *1:* 64
McNerney, J. M., *2:* 324
Machado, A. B. M., *1:* 313
Mackler, B., *7:* 129
Magee, A. C., *3:* 71
Magner, J. M., *2:* 362
Main, R. J., *5:* 12
Makepeace, L. I., *1:* 254
Malherbe, H., *2:* 249
Malhotra, W. P., *2:* 355
Malm, O. J., *1:* 475
Mameesh, M. S., *3:* 72
Mandl, A. M., *4:* 52
Mangold, W. S., *6:* 12
Mannering, G. J., *3:* 8
Mantel, N., *1:* 327
Mardones, E., *2:* 340

Margolis, G., *6:* 48
Markowitz, J., *7:* 172
Marr, A. G., *1:* 291
Marsh, D. F., *7:* 26
Marshall, F. H. A., *1:* 4
Marshall, L. H., *1:* 214, 255
Marshall, R. J., *1:* 480
Martens, H. H., *1:* 388
Martin, W. R., *7:* 136
Martin, W. S., *1:* 70
Martinez, C., *1:* 191
Mason, M. M., *1:* 481
Mason, W. A., *7:* 173
Massion, W. H., *1:* 309
Masson, G. M. C., *1:* 130
Mathé, G., *1:* 400
Mathews, E. D. J., *5:* 70
Mathews, J., *2:* 374
Mathis, M., *4:* 6
Matrone, G., *3:* 71
Mattie, L. R., *1:* 367
Mattis, P. A., *7:* 191
Maurer, F. D., *2:* 250, 251
Mawson, C. A., *2:* 252
May, A. J., *1:* 249
Maykut, M. O., *7:* 141
Mayer, J., *1:* 173, 341, 418
Mayer, K., ed., *2:* 178, 330, 348
Maynard, F. L., *6:* 29
Maynard, L. A., *3:* 40
Mebust, W., *1:* 336
Medeci, P. T., *1:* 492
Medoff, H. S., *1:* 58
Meessen, H., *2:* 207
Mefferd, R. B., Jr., *1:* 385–389, 456
Meier, H., *2:* 373
Meinken, M. A., *1:* 90
Meites, J., *4:* 110
Meli, A., *1:* 126
Meltzer, M. R., *7:* 142
Melzack, R., *1:* 264
Menges, R. W., *2:* 163, 248, 343
Menzies, W., *4:* 107
Merchant, I. A., *2:* 114
Merck & Co., *2:* 42, 55
Merck Veterinary Manual, *2:* 83
Metcoff, J., *1:* 53
Mewaldt, L. R., *1:* 140
Meyer, K. F., *2:* 43
Meyer, L. M., *1:* 74
Meyer, R. de, *1:* 339
Meyer, R. K., *7:* 6
Michael, R. P., *1:* 390
Michaelson, I. C,. *1:* 192
Michie, D., *1:* 190, 330; *4:* 53, 75
Michieli, R., *5:* 120
Middleton, M. J., *1:* 365
Mikiskau, A., *7:* 88
Millar, M. J., *2:* 252
Millen, J. W., *2:* 179
Miller, A. T., Jr., *1:* 78, 233
Miller, B. F., *2:* 286
Miller, M. A., *1:* 224
Miller, M. E., *1:* 113
Miller, O. T., *5:* 82
Millman, N., *1:* 416
Mills, C. A., *1:* 14, 15, 36, 47, 59; *2:* 10, 13; *3:* 10; *5:* 19
Mills, M., *2:* 13
Mirsky, A. E., *1:* 427
Mishkin, M., *7:* 174
Misler, S., *3:* 84
Mitchell, P. C., *6:* 10
Mittelstaedt, S. G., *2:* 279
Miyakawa, M., *1:* 482; *4:* 108
Moak, S. J., *7:* 185
Mock, J. F., *8:* 15
Möbest, H., *1:* 391
Mogenson, G. J., *1:* 314
Mohr, W., *2:* 203
Moinuddin, J. F., *1:* 483; *2:* 244
Mondini, S., *1:* 315
Montagna, W., *1:* 137
Moore, B., *2:* 180
Moore, E. B., *7:* 190
Moore, E. N., *1:* 354
Moore, F. D., *7:* 186
Morgan, C. F., *6:* 31
Morgan, H. C., *2:* 344
Morgan, P. V., *4:* 38
Morley, E. H., *1:* 217
Morrill, C. C., *2:* 11
Morris, E. R., *2:* 258
Morris, H. P., *1:* 151; *3:* 4
Morris, M. L., *2:* 345, 346
Morrison, F. B., *3:* 18
Morrison, P. R., *1:* 66
Moser, C. E., *7:* 30
Mosher, R., *1:* 517
Motsavage, M. A., *2:* 217
Mott, J. C., *1:* 443
Moulton, F. R., *2:* 16
Moulton, J. E., *2:* 303
Mouromseff, G., *5:* 71
Mouton, D., *1:* 279
Mucha, A., *7:* 191
Mühlbock, O., *6:* 49
Mühlemann, H. R., *1:* 183
Mueller, A. J., *1:* 26
Mueller, L. F., *6:* 34
Müller-Beuthow, W., *1:* 246
Mullican, C. L., *5:* 101
Mulligan, R. M., *1:* 60; *2:* 25
Mulligan, W., *2:* 312
Munday, V., *2:* 249
Mundy, A. E., *4:* 39; *8:* 4
Munkelt, F. H., *5:* 22
Munn, N. L., *1:* 87
Munson, P. L., *2:* 369
Murayama, M., *1:* 392

Nachtwey, D. S., *8:* 5
Nadel, E. M., *1:* 484
Naess, K., *7:* 143
Nagy, R., *5:* 71
Nakashima, M., *1:* 364
Nakayama, F., *7:* 175
Nalbandov, A. V., *1:* 393
Nardone, R. M., *1:* 460
Nathan, D. G., *1:* 485
National Academy of Sciences, *see* National Research Council
National Research Council, *9:* 17
  Agricultural Board, *6:* 17
  Committee on the Handbook of Biological Data, *1:* 114, 256, 394, 486; *2:* 347; *3:* 35
  Institute of Laboratory Animal Resources, *4:* 65; *6:* 58; *9:* 13
  Committee on Animal Care, *6:* 59
  Committee on Handbook, *4:* 45
  Committee on Standards, *4:* 76, 109
National Society for Medical Research, *9:* 5
National Vitamin Foundation, *1:* 151
Naumann, G., *1:* 512
Nay, T., *1:* 193
Necheles, H., *1:* 479
Needham, J. G., *4:* 4
Neely, W. A., *1:* 487
Negherbon, W. O., *2:* 347
Neher, G. M., *2:* 253
Nelson, J. B., *1:* 151; *2:* 181, 254; *4:* 19
Nelson, N., *5:* 41
Nelson, V. E., *2:* 3
Netsky, M. G., *2:* 306
Neufeld, E. F., *1:* 104
Neuman, W. F., *1:* 202
Newberne, J. W., *2:* 348
Newberne, P. M., *2:* 255
Newman, B. J., *5:* 120
Newton, W. L., *2:* 349
Nicholas, J. S., *1:* 73; *5:* 8
Nichols, J., *1:* 78
Nichols, J. E., *4:* 54
Nick, R. T., *6:* 34
Nicoll, C. S., *4:* 110
Nielsen, K., *5:* 16
Nigrelli, R. F., *2:* 86
Nikolitsch, M., *2:* 256, 257
Nikoloff, P., *1:* 270
Nishihara, H., *1:* 510
Niven, J. S. F., *2:* 91, 164
Njaa, L. R., *4:* 77
Noble, R. L., *2:* 350
Norris, W. P., *7:* 60
North, J. D. K., *2:* 115
Northcote, D. H., *3:* 29
Norton, H. W., *2:* 355
Noyes, H. E., *7:* 176
Noyes, R. W., *1:* 395
Nyman, M. A., *1:* 389

Obel, N., *7:* 132
O'Dell, B. L., *2:* 255, 258
Oettle, A. G., *1:* 350
Ogawa, T., *1:* 479
Ogle, C. L., *1:* 14, 15, 16, 23, 36
Ohlander, A., *1:* 329
Oldfield, J. E., *3:* 52
Olmsted, F., *1:* 130
Olsen, L. S., *4:* 118
Olson, W. H., *1:* 38
Olsson, B., *3:* 43
O'Meara, D. C., *2:* 140
Orkin, M., *2:* 351
Orland, F. J., *6:* 60
Ormiston, D. W., *7:* 177
Orten, J. M., *5:* 6
O'Steen, W. K., *2:* 169
Otis, A. B., *7:* 102
Ott, M., *1:* 55

Packer, R. A., *2:* 114
Padula, J. F., *2:* 283
Pagé, E., *1:* 199
Page, K. W., *2:* 44
Palmer, C. E., *2:* 299
Panchenko, L. F., *7:* 144
Pankevicius, J. A., *4:* 72
Pantelouris, E. M., *1:* 316
PapaMichael, A., *3:* 82
Pappenheimer, A. M., *2:* 21, 259, 260, 261
Pareira, M. D., *1:* 488
Parish, H. J., *2:* 27
Parizek, O., *7:* 88
Park, J. T., *3:* 78
Parker, H. R., *4:* 100
Parkes, A. S., *1:* 396; *3:* 14; *4:* 12; *5:* 72
Paronetto, F., *1:* 412
Parrish, D. B., *3:* 66
Parrish, H. M., *8:* 15
Parrott, D. M. V., *1:* 381
Parsons, J., *1:* 271
Parvin, J. R., *2:* 56
Paschkis, K. E., *1:* 262, 351
Paterson, J. S., *2:* 116; *3:* 57; *4:* 33, 40; *8:* 12
Patterson, G. N., *1:* 163
Pauly, J. E., *1:* 489
Payne, L. C., *1:* 159
Peacock, L. J., *1:* 490
Pearce, L., *1:* 8
Pearce, W. M., *1:* 381
Pearson, A. M., *7:* 138
Pearson, O. P., *1:* 66
Peck, H. M., *1:* 275
Peo, E. R., *4:* 118
Perdue, H. S., *2:* 120
Pereira, W. P., *5:* 44
Perez Gallardo, *2:* 262
Perk, K., *1:* 491
Perkins, F. T., *5:* 100
Perlman, E., *2:* 119
Perlman, P. L., *2:* 328
Perry, J. S., *4:* 55
Petersen, E. S., *1:* 103
Petrie, S. J., *7:* 29
Pfizer, C., & Co., *3:* 1
Phillips, B. P., *2:* 352; *4:* 111
Phillips, G. B., *2:* 117; *5:* 82, 92, 101
Phillips, P. H., *2:* 120
Pickering, J. E., *2:* 243
Pienaar, U. de V., *1:* 98
Pike, R. M., *8:* 3
Piliero, S. J., *1:* 492
Pinsky, J. J., *1:* 240
Pitesky, I., *7:* 27
Pittaway, E. M., *1:* 397
Plachta, A., *1:* 492
Platts, T. L., *7:* 59
Pleasants, J. R., *3:* 85; *4:* 117
Pockson, A. P., *4:* 66
Podleski, T. R., *1:* 382
Podliachouk, L., *1:* 176
Poiley, S. M., *1:* 151; *4:* 1, 26
Pomeranze, J., *1:* 492
Poncelet, J., *1:* 230
Pool, W. A., *2:* 353
Porter, G., *8:* 13
Posternak, J., *7:* 19
Poth, E. J., *3:* 7

Pratt, D. A. H., *7:* 146
Prediger, R. F., *7:* 80
Prentiss, P. G., *3:* 86
Pribilla, W. F., *1:* 336
Price, W. T., *4:* 27
Prichard, R. W., *2:* 306
Princi, F., *7:* 28
Pritchard, W. R., *1:* 404
Proctor, D. F., *7:* 102
Prosser, L., *1:* 115
Pruett, D., *2:* 126
Pye, O. F., *3:* 87
Pyle, N. J., *1:* 39

Quimby, F. H., *1:* 79, 328
Quinlin, P. M., *1:* 90
Quiring, D. P., *1:* 37

Rabinovitz, M. J., *1:* 426
Rabstein, M. M., *5:* 121
Radford, E. P., Jr., *1:* 493
Ragsdale, A. C., *1:* 379
Raica, N., *3:* 58
Ralston Purina Co. Research Laboratories, *5:* 57
Ramsay, A. G., *3:* 25; *5:* 23
Ranadive, K. J., *3:* 59
Ranson, R. M., *1:* 10
Rapoport, S., *1:* 92
Rask-Nielsen, R., *1:* 461
Rasmussen, E. W., *7:* 143
Ratcliffe, H. L., *2:* 17, 36, 70; *5:* 19
Raven, H. C., *1:* 88
Ray, A., *2:* 354
Ray, A. P., *3:* 61
Ray, T. W., *5:* 13
Read, C. P., *2:* 214
Reber, E. F., *2:* 355
Rebrassier, R. E., *2:* 6
Rees, O., *2:* 206
Rees, R. J. W., *2:* 39
Regan, W. O., *2:* 258
Register, U. D., *1:* 120
Reid, M. E., *3:* 73, 74
Reighard J., *1:* 18
Reineke, E. P., *1:* 116, 269; *7:* 138
Reitman, M., *2:* 117; *5:* 101
Renaud, S., *7:* 178
Renoux, G., *2:* 182
Reyniers, J. A., *2:* 356, 365; *4:* 78, 95, 112, 113; *5:* 17, 18
Reynolds, H. C., *1:* 160
Rhode, E. A., *2:* 209
Rhodes, B., *7:* 37
Richardson, F. L., *2:* 357
Richter, A. W., *7:* 134
Richter, C. P., *3:* 19
Ricketts, H. T., *1:* 103
Riedesel, M. L., *1:* 317, 398
Rigdon, R. H. *2:* 358
Riopelle, A. J., *1:* 399
Riser, W., *2:* 71
Ritchie, A. C., *2:* 58
Rivlin, R. S., *1:* 476
Rixton, F. H., *5:* 71
Robbins, A. F., *7:* 84
Roberson, W. J., *1:* 248, 250
Roberts, C. S., *2:* 163
Roberts, J. R., *7:* 129
Robinson, H. W., *1:* 101
Robscheit-Robbins, F. S., *4:* 28
Robson, D. S., *2:* 230, 293
Robson, M. J., *2:* 201
Roddick, B. J., *7:* 145
Roepke, M. H., *2:* 222
Rogers, C. M., *1:* 490
Rohles, F. H., Jr., *7:* 177, 179
Rojas, G., *2:* 340
Romer, A. S., *1:* 257
Rosa, J., *1:* 400
Roscoe B. Jackson Memorial Laboratory, *9:* 12, 19
Rose, C. L., *1:* 67; *7:* 14
Rosen, S., *2:* 288
Rosenberg, A. J., *7:* 180
Rosenthal, H. L., *1:* 494
Rosenthal, S. R., *7:* 181
Rosenzweig, M. R., *1:* 329
Ross, M. A., *4:* 72, 96
Ross, S., *1:* 318, 352
Rosvold, H. E., *7:* 174
Rothschild, P., *7:* 8
Rothstein, N., *2:* 359
Roveda, R. J., *2:* 59
Rowe, F. P., *1:* 348
Rowlands, I. W., *4:* 41, 56, 97
Rubadeau, D. O., *1:* 157
Rubin, M. L., *2:* 263
Ruch, T. C., *1:* 43; *2:* 14, 360
Rucker, R. R., *2:* 56
Ruddy, J. M., *5:* 45
Rude, F. R., *7:* 180
Ruegamer, W. R., *1:* 194, 258
Rugh, R., *4:* 20
Rumery, R., *1:* 333
Runnells, R. A., *2:* 72
Runner, M. N., *1:* 295
Russell, E. S., *1:* 104, 124, 220, 401; *4:* 65
Russell, W. M. S., *8:* 16
Ryan, H., *1:* 180
Ryckman, R. E., *7:* 61
Ryd, H., *7:* 72
Ryder, H. W., *1:* 91

Sabourdy, M., *5:* 73; *8:* 14
Sachs, W. B., *5:* 46
Sacksteder, M. R., *2:* 356; *4:* 95
Sacquet, E., *2:* 182
Sadhu, D. P., *2:* 354
Safier, L. B., *1:* 471
Saifer, A., *1:* 502
St. George-Grambauer, B. M., *2:* 264
St. Pierre, J., *1:* 300
Sainte-Marie, G., *1:* 402
Salaman, M. H., *2:* 118
Salerno, R. A., *7:* 182
Salzano, J., *1:* 495
Sand, B. F., *7:* 106
Sandberg, F., *7:* 73
Santmyer, P. H., *2:* 362
Sapirstein, L. A., *1:* 496
Sargent, F., II, *1:* 448
Sarkar, S., *2:* 205
Sarles, M. P., *2:* 45
Saunders, C. G., *2:* 1
Saunders, L. Z., *2:* 265, 266, 267, 321
Sautter, J. H., *1:* 404
Sawin, P. B., *1:* 310, 352; *4:* 21
Sawitsky, A., *1:* 74
Saxon, P. A., *1:* 79
Saxton, J. A., Jr., *2:* 18
Scarborough, R. A., *1:* 12
Scarnell, J., *4:* 42
Schaedler, R. W., *2:* 218
Schaefer, H. C., *2:* 144
Schaffenburg, C. A., *7:* 183
Schalm, O. W., *1:* 500
Schapira, G., *1:* 400
Schermer, S., *1:* 403
Schild, H. O., *7:* 79
Schilling, J. A., *1:* 309
Schirmer, R. G., *2:* 183
Schlang, H. A., *7:* 184
Schloerb, P. R., *1:* 434
Schlosser, C., *5:* 114
Schlotthauer, C. F., *6:* 13
Schmidt, H., Jr., *7:* 185
Schmidt, I. G., *1:* 31
Schmidt, L. H., *1:* 47
Schmidt, W. J., *1:* 24
Schmitt, R. F., *5:* 82
Schneider, H. A., *2:* 57
Schneierson, S. S., *2:* 119
Schneyer, C. A., *1:* 497
Schneyer, L. H., *1:* 497
Schroeder, C. R., *2:* 7
Schroeder, M. A., *2:* 201
Schultze, M. O., *2:* 104
Schwarte, L. H., *2:* 298
Schwartz, B., *2:* 4
Schwartz, R., *2:* 148
Schwartzman, R. M., *2:* 351
Schwarz, J., *2:* 50, 73
Schwentker, V., *5:* 84, 91, 122
Scott, H. G., *2:* 268
Scott, J. P., *1:* 319
Scott, M. G., *2:* 269
Scott, M. L., *2:* 98
Scott, P. P., *2:* 269; *3:* 60
Scott, T. H., *1:* 264
Scribner, G. M., *5:* 80
Scrimshaw, N. S., *1:* 195; *2:* 361
Seifried, O., *7:* 5
Sellar, R. F., *1:* 498
Sellers, A. F., *1:* 404
Selye, H., *5:* 16; *7:* 62
Sembower, J. F., *6:* 63
Semellini, L., *2:* 184
Semler, H. J., *1:* 480
Sérié, C., *2:* 76
Serkes, K. D., *1:* 488
Shapiro, H., *4:* 79
Sharp, C. F., *2:* 270
Shohmeister, I. L., *5:* 131
Shorey, B. E., *4:* 80
Shelesnyak, M. C., *7:* 51
Shelton, G. C., *2:* 362
Shepherd, E. L., *2:* 368
Shepherd, J. T., *1:* 480
Shils, M. E., *1:* 151
Shock, N. W., *1:* 277
Shoemaker, W. C., *7:* 186
Shook, W. B., *2:* 5
Short, D. J., *3:* 88; *5:* 74, 100
Shrewsbury, M. M., *1:* 405
Shubik, P., *2:* 58
Shukers, C. F., *1:* 32
Shumacker, H. B., Jr., *1:* 24
Shuster, S., *1:* 136
Sidransky, H., *2:* 271
Silberberg, M., *2:* 272
Silberberg, R., *2:* 272, 273
Silverman, F. R., *1:* 258
Simmonds, J. P., *1:* 5
Simmons, J. S., *7:* 81
Simmons, V. P., *7:* 187
Simon, A. B., *1:* 230
Simon, J., *2:* 61
Simpson, M., *1:* 180
Sinclair, H. M., *2:* 115
Singer, M., *7:* 71
Singh, J., *3:* 61
Skupp, S. J., *1:* 471
Slanetz, C. A., *1:* 151; *2:* 23, 274; *3:* 17, 20, 62, 89; *5:* 75; *6:* 41
Sloan, R. F., *7:* 161
Sloss, M. W., *2:* 75, 308
Smart, J. V., *1:* 498
Smith, A. H., *5:* 5
Smith, A. U., *1:* 241
Smith, C., *4:* 81
Smith, D. C., *6:* 32
Smith, D. L., *2:* 151
Smith, E., *1:* 259
Smith, E. L., *1:* 374; *2:* 314
Smith, G. D., *7:* 98
Smith, G. R., *2:* 363
Smith, H. A., *2:* 185
Smith, H. M., *2:* 364
Smith, J. K., *5:* 76
Smith, O. A., Jr., *7:* 188
Smith, R. T., *1:* 446
Smith, V. H., *7:* 147
Smyth, D. H., *8:* 9
Smyth, H. F., *6:* 61
Smythe, R. H., *1:* 260
Snell, G. D., *1:* 44
Soave, O. A., *6:* 33
Sobek, V., *2:* 275
Sober, H. A., *3:* 8
Sohar, E., *1:* 412
Sokoloff, L., *2:* 276, 277
Soliman, F. A., *1:* 116, 261
Somers, G. F., *7:* 70
Sosnow, M., *7:* 56
Southwick, C. H., *5:* 132
Spanier, M. R., *1:* 155
Sparer, R., *3:* 82
Spaulding, E. H., *1:* 101
Spector, H., *1:* 517
Spector, W. S., *1:* 256; *2:* 347
Sperling, G., *3:* 31, 51
Spiegl, C. J., *7:* 137
Spivey, H. E., *3:* 70
Spörri, H., *1:* 368
Spray, C. M., *1:* 89
Spray, G. H., *1:* 406
Sprent, J. F. A., *2:* 278
Springer, G. F., *1:* 499
Spurr, G. B., *1:* 154
Spurrier, W. A., *7:* 181
Squibb, R. L., *1:* 195
Sriramachari, S., *2:* 216
Staats, J., *1:* 407
Stagg, R. D., *7:* 89
Stalker, A. L., *2:* 186
Stanger, R. L., *1:* 416
Stanley, W. M., *2:* 301
Steel, J. M., *3:* 69
Steinmetz, W. H., *5:* 84

Steldt, F. A., *2:* 10
Stellar, E., *3:* 90
Stephen, C. R., *6:* 48
Stephenson, H. C., *2:* 279
Stetten, D., Jr., *1:* 217
Stevens, C. D., *1:* 90
Stevens, C. E., *1:* 262
Stevens, G. E., *1:* 154
Stevenson, G. T., *2:* 90
Stewart, J. D., *7:* 67
Stewart, P. B., *1:* 408
Stewart, P. H., *1:* 90
Stewart, R. J. C., *6:* 42
Stiffel, C., *1:* 279
Stiles, S. W., *7:* 189
Stilinović, Z., *2:* 103
Stoenner, H. G., *2:* 280
Stone, A., *7:* 56
Stoufer, R. M., *4:* 72
Strange, N., *5:* 77
Stratton, K., *7:* 123
Straub, O. C., *1:* 500
Straus, W. L., Jr., *1:* 13
Street, H., *6:* 4
Streicher, E., *1:* 409
Strong, L. C., *1:* 410
Sudak, F. N., *1:* 163
Suitor, A., *3:* 15
Sulkin, S. E., *2:* 187; *8:* 3
Sultz, F. T., *2:* 194
Summer, W., *5:* 58
Sumption, L. J., *4:* 118
Sunderman, F. W., *1:* 262; *7:* 90
Sundstroem, E. S., *1:* 6
Switzer, J., *1:* 439
Sykes, J. A., *7:* 190
Syverton, J. T., *7:* 11

Tajima, Y., *2:* 170
Takano, G. M. V., *3:* 22
Taketa, F., *2:* 120
Talalay, P., *3:* 22
Tang, Y.-Z., *3:* 3
Tarver, H., *1:* 127
Taskar, A. D., *1:* 235
Taylor, A. R., *2:* 365; *6:* 62
Taylor, C. E., *2:* 361
Taylor, C. M., *3:* 87
Taylor, J., *2:* 121
Taylor, K. B., *1:* 406
Tedeschi, D. H., *7:* 191
Tedeschi, R. E., *7:* 191
Temple, L. A., *7:* 147
Templeton, G. S., *3:* 15; *4:* 58
Teodoru, C. V., *1:* 501, 502
Terry, M. W., *2:* 360
Test, C. E., *1:* 103
Teuscher, E., *2:* 188
Theilen, G. H., *1:* 500; *2:* 209
Thomasson, R., *2:* 273
Thompson, H. V., *1:* 263
Thompson, J. S., *2:* 201
Thompson, J. W., *3:* 4
Thompson, S. W., *2:* 366
Thompson, W. R., *1:* 196, 264, 320, 411
Thorbecke, G. J., *1:* 503, 504
Thorp, W. T. S., *2:* 66; *5:* 29, 59; *6:* 63
Thorsteinsson, T., *1:* 345
Thrailkill, F. B., *2:* 280
Thuillier, J. E., *7:* 48
Timiras, P. S., *1:* 134
Tipton, S. R., *1:* 143
Tockes, I. M., *2:* 213
Tolki, R., *1:* 391
Totton, M., *2:* 281
Trahan, H., *7:* 181
Trapani, I. L., *1:* 505
Traum, R. E., *1:* 349
Treon, J. F., *1:* 91
Trexler, P. C., *4:* 99, 114
Trowell, O. A., *7:* 192
Tubis, M., *2:* 200
Tuffery, A. A., *2:* 122
Tuke, W., *5:* 112
Tupikova, N. A., *1:* 103
Turner, C. W., *1:* 244, 431, 454
Turner, M. L., *1:* 64

Udall, R. H., *2:* 26; *3:* 30
Umbreit, W. W., *1:* 253
Underdahl, N. R., *4:* 118
Underhill, F. A., *5:* 6
Ungar, G., *2:* 15
United States
  Dept. of Agriculture, *2:* 123, 367; *4:* 115; *9:* 3
  Depts. of Army and Air Force, *5:* 123
  Federal Trade Commission, *6:* 50
  National Institutes of Health, Surgery Study Section, *5:* 24
  Public Health Service, *7:* 193; *9:* 20
University of California, Committee on Animal Care, *5:* 2
Unna, K. R., *7:* 136
Unruh, W., *2:* 226
Urbach, E., *2:* 19
Utne, F., *4:* 77

Vallejo-Freire, A., *7:* 34
Van Bekkum, D. W., *1:* 415
Van Bruggen, J. T., *5:* 47
Vandegrift, W. B., *2:* 45
Vandepopuliere, J. M., *2:* 144
Van Dijck, P., *2:* 153
Van Itallie, T. B., *7:* 186
Van Loon, E. J., *1:* 51
Varney, P. L., *6:* 5
Vavich, M. G., *3:* 58
Vawter, G. F., *1:* 456; *2:* 243
Veenstra, R. J., *4:* 70
Venard, C. E., *2:* 8
Venturoli, M., *1:* 315
Venzke, W. G., *1:* 354
Vesselinovitch, S. D., *1:* 506
Vincent, D. J., *2:* 287
Visscher, M. B., *1:* 182
Vitale, D., *1:* 430
Voge, M., *2:* 282
Vogel, H., *2:* 189
Vogel, M., *1:* 75
Vogel, R. A., *2:* 283
Volf, V., *5:* 124
Von Brand, T., *2:* 143

Wada, T., *1:* 1
Wadlund, A. P. R., *1:* 9
Wagner, M., *1:* 507, 508
Wagshal, R. R., *7:* 40
Waisimen, H. A., *3:* 9
Wakerlin, G. E., *1:* 25
Wald, N., *1:* 383; *2:* 175, 338
Walker, A. E., *1:* 33
Walker, D. O., *1:* 321
Walker, G., *6:* 6
Walker, W. F., *7:* 186
Wallace, C. R., *2:* 141
Wallis, A. T., *7:* 124
Wallis, C., *2:* 187
Walsh, J. M., *1:* 426
Walter Reed Army Institute of Research, Div. of Veterinary Medicine, *4:* 82
Walton, A., *1:* 395
Wang, C., *1:* 412
Warner, R. G., *3:* 31
Warnock, N. H., *1:* 285
Warren, K. S., *1:* 485
Waterhouse, C. E., *5:* 103
Watson, D., *7:* 146
Watson, D. F., *1:* 323
Watts, D. T., *1:* 161
Webb, C., *1:* 359
Webb, J. E., Jr., *2:* 368
Weber, A. F., *1:* 404
Webster, G. A., *2:* 284
Webster, S. H., *1:* 76, 84
Webster, W. W., *1:* 389
Wedum, A. G., *5:* 92
Weeks, G. G., *3:* 63
Weeth, H. J., *4:* 91
Wegelius, O., *1:* 509
Wegmann, H., *1:* 368
Weil, A. J., *1:* 413
Weimer, H. E., *1:* 510
Weinbaum, M., *3:* 82
Weiner, D., *2:* 285
Weininger, O., *1:* 197
Weinstein, P. P., *2:* 349
Weipers, W. L., *2:* 124
Weiss, C., *5:* 125
Weiss, S. M., *5:* 33
Weitz, B. G. F., *5:* 78; *8:* 12
Welbourn, R. B., *1:* 356
Welch, P. S., *4:* 4
Wellers, G., *1:* 265, 414
Welling, W., *1:* 415
Wells, H., *2:* 369
Wells, W. F., *5:* 83
Wenke, M., *2:* 275
West, C. D., *1:* 92
West, G. B., *6:* 29
Westrick, M. L., *2:* 324
Weydert, K. A., *6:* 51
Wexler, B. C., *2:* 286
Whipple, W. J., *2:* 56
Whitaker, W. L., *7:* 12
Whitehill, A. R., *3:* 49
Whitehouse, J. M., *7:* 121
Whitehouse, R. H., *1:* 266
Whiteside, W. H., *2:* 28
Whitfield, F. G. S., *5:* 86
Whitney, L. F., *1:* 162
Whitten, H., *1:* 511; *5:* 133
Whitten, W. K., *2:* 125; *4:* 67, 116
Wichmann, R. W., *2:* 287
Wickert, W. A., *2:* 288
Widdicombe, J. G., *1:* 249
Widdowson, E. M., *1:* 89
Widelock, D., *2:* 189
Wigand, R., *2:* 289
Wiggers, H. C., *1:* 155
Wilde, J., *1:* 512
Wildführ, G., *1:* 512
Wilgram, G. F., *2:* 370
Willard, D. H., *7:* 147
Wille, H., *1:* 153
Williams, E. M. V., *1:* 68
Williams, F. P., Jr., *2:* 66, 165, 166, 190, 235, 236
Wills, J. H., *1:* 211
Wilson, C. E., *4:* 72, 96
Wiltbank, J. N., *2:* 61
Winchester, C. F., *3:* 32
Winn, J. F., *2:* 371
Winters, L. M., *4:* 44
Wintrobe, M. M., *1:* 24
Wirtschafter, Z. T., *1:* 321
Wislocki, G. B., *1:* 340
Wissler R. W., *2:* 201
Witherup, S., *7:* 23
Witschi, E., *1:* 267
Witte, E. J., *2:* 341
Woke, P. A., *7:* 35
Wolf, A. V., *3:* 86
Wolf, N. S., *2:* 74
Wolfe, H. G., *1:* 513
Wolfe, P. A., *2:* 352
Wood, A. J., *1:* 276
Woodley, C. H., *1:* 437
Worden, A. N., *1:* 263; *3:* 33; *5:* 102, 103
Wostmann, B. S., *1:* 514, 515; *3:* 91; *4:* 117
Wright, J. F., *2:* 372
Wulf, H., *7:* 5
Wulff, H. B., *7:* 72
Wyman, L. C., *1:* 163

Yager, R. H., *6:* 24
Yeates, N. T. M., *4:* 46
Yen, H. C. Y., *1:* 416
Yerganian, G., *2:* 373
Yevich, P. P., *4:* 72
Yiengst, M. J., *1:* 277
Yoffey, J. M., *1:* 47; *6:* 56
Yost, D. H., *2:* 290
Young, B. G., *1:* 484
Young, D. R., *1:* 516, 517
Young, D. W., *1:* 458
Young, F. A., *5:* 134; *7:* 109
Young, G. A., *4:* 118
Young, M. W., *1:* 422
Young, R. J., *2:* 158, 191; *5:* 61, 104; *8:* 5
Young, W. A., *2:* 46; *5:* 34
Young, W. C., *1:* 272, 296, 301; *2:* 241

Zackin, S. J., *2:* 369
Zander, H. A., *1:* 183
Zangwill, O. L., *1:* 417
Zarrow, M. X., *1:* 303
Zarzuelo, E., *2:* 262
Zausch, M., *7:* 83
Zeigen, R. S., *7:* 162
Zimmer, D. J., *1:* 76
Zimmermann, W. J., *2:* 374
Zomzely, C., *1:* 418
Zucker, L. M., *1:* 69, 151
Zucker, T. F., *1:* 69, 151; *2:* 192; *4:* 29
Zuidema, G. D., *7:* 98
Zweifach, B. W., *2:* 375

Subject index

This index represents an analysis of the contents of the abstracts. Material pertaining to the normal anatomy, physiology, psychology of animals, and their variation or modification by age, sex, or environment, is indexed under the specific kind of animal, or under the broad classes of *Animals*, *Domestic animals*, *Laboratory animals*, etc. The effects of the manipulation of environmental factors, such as handling, temperature, population dynamics (crowding, isolation), etc., are also cross-indexed under the specific factor. Pathologic conditions are entered under *Diseases* by type of disease, system involved, or type of agent. The scientific names of agents causing disease, as well as of animals and of some species and breeds, are cross-indexed under the appropriate name, where and as given in the abstract (in the terminology of the author), without further description. The practical aspects of the production and management of animals are handled under *Breeding*, *Diets*, *Handling*, *Housing*, etc. Techniques are entered under the specific type of technique, such as *Blood pressure measurement*, *Injection*, etc. This applies also to the type of research in which animals are used.

Books and pamphlets, bibliographies, conferences and symposia, and periodicals are entered with the title under *Books and pamphlets*, etc., as well as under the specific kind of animal, or broad classes of *Animals*, *Domestic animals*, etc., according to the subject matter as designated in the title only. Their contents, as covered in the abstract, are cross-indexed usually broadly under the specific kind of animal, where they are so indicated. Texts on anatomy or physiology are generally indexed by the broad terms of "*anatomy*," "*physiology*," under the kind of animal or group of animals.

"See" references, in capitalized words, indicate entries under main alphabetical sequence; those in lower case, enclosed in quotation marks, refer to entries under the capitalized heading.

The abstract numbers are designated in the same manner as in the *Author Index*.

Acaricide tests, use of mouse in, *2:* 318
Acetylcholine, sensitivity of rat to, *7:* 70
Activity
  cages, *1:* 157, 175; *7:* 188
  study of, *see* Behavior study techniques; Physical activity measurement techniques
Administration of laboratory animal colonies, *4:* 50; *5:* 123; *8:* 9, 14
  see also Costs; Personnel; Procurement; Records; Sources of supply
  central care, *8:* 8
  decentralization of units, *5:* 87
  relation to research division, *8:* 10
Adrenal gland function tests
  for function in animals, *see under* specific kind of animal
  in dog, *1:* 335
  in mouse, *7:* 167
  steroid analysis by paper chromatography, *1:* 141
Adrenalectomy
  effect on mouse, *1:* 150
  effect on rat, *1:* 351; *7:* 121
  technique, in rat, *7:* 139
Adrenocorticoid excretion research
  use of animals in, *1:* 106
Age determination
  in domestic animals, post-mortem, *7:* 100
  in laboratory animals, *7:* 58
  in rat, *1:* 436
Air conditioning, purification, sterilization, in animal quarters, *see under* Housing
Airborne contagion
  and air hygiene, *5:* 83
  transmission of bacterial infection, *2:* 117
Alcaligenes bronchiseptica, *2:* 326
Allergic diseases, *see under* Diseases
Allergy production in guinea pig, by inhalation, *7:* 32
Altitude, effects of
  on dog, *1:* 228
  on rabbit, *1:* 505
  on rat, *1:* 206, 347, 385, 387, 388, 389, 420, 421
Amebiasis research, use of germfree guinea pig in, *2:* 352
Amphibia
  see also Frog; Salamander; Toad
  body, organ, gland weights, *1:* 37
  care and management of, *5:* 27, 102, 133
  carotid body and sinus; anatomy, macro- and microscopic, embryology, physiology, *1:* 322
  circulatory system, *1:* 486
  nervous system, anatomy, *1:* 21
Anatomical research
  use of rat in, *3:* 19
  for anatomy of animals, *see under* specific kind and groups of animals; for texts on, *see* Books and pamphlets
Anesthesia
  see also Sedatives; Soporific drugs; Tranquilizers
  administration, action, danger, *7:* 99
  anesthetics for
    animals, effects on blood, *1:* 12
    cat, *5:* 34
      barbiturates, and antidote against, *7:* 110
        evaluation of methitural vs. thiopental, *7:* 89
      ether, technique, *7:* 189
      trichloroethylene, *7:* 113
    cattle
      nitrous oxide with barbiturate and succinyl choline; apparatus with respirator, *7:* 131
    chicks
      barbiturates, *7:* 96
    dog, *2:* 178
      barbiturates
        effects on blood, *1:* 184; *2:* 314
        evaluation of methitural vs. thiopental, *7:* 89
        intramuscular, intraperitoneal, *7:* 112
        morphine, and; premedication, *7:* 151
        nitrous oxide, and; premedication, artificial respiration, *7:* 130
      electric current, *7:* 4
      halothane, evaluation, *7:* 170
      spinal, *7:* 4
    guinea pig
      barbiturates

Anesthesia (*continued*)
intravenous, *7:* 133
procaine and derivatives, subcutaneous, *7:* 141
local, and effects on nervous system and skin, *7:* 141
horse
nitrous oxide with barbiturate and succinyl choline; apparatus with respirator, *7:* 131
monkey
barbiturates; evaluation of methitural vs. thiopental, *7:* 89
mouse
chloroform
effects on blood of inbred, *1:* 124
effects on kidney of inbred; pathology; strain variation, *2:* 49
effects on kidney; pathology; sex variation; effects of castration, *2:* 167
ether, fluothane, trichloroethylene;
effect on liver; pathology, *6:* 48
toxicity for, *2:* 49, 58, 167
effects on body temperature of inbred, in cold, *1:* 119
ether, *2:* 310
mask for, *7:* 16
parakeet
Equithesin, intramuscular, *2:* 321
rabbit, *2:* 135
barbiturates, urethane, *7:* 103
chlorpromazine and, intravenous, *7:* 159
ether, urethane; hazards of, *7:* 108
curarization with rectal suppository, *7:* 48
rat, *1:* 45
barbiturates
chlorpromazine; effects on water intake, *7:* 185
effects on basal metabolism, *1:* 161
glucose and, *7:* 36
phenothiazines and, *7:* 185
ether, open drop technique, *7:* 139
mask for, *7:* 16
antagonists and antidotes for, *7:* 110, 151
blood pressure measurement during, in dog, cattle, horse, *7:* 132
humane technique in laboratory, *7:* 99
inhalation
automatic method, *7:* 98
equipment for, *7:* 16, 69, 131, 161
reviews, *2:* 69, 172; *5:* 8, 102; *7:* 164
toxicity tests, use of mouse in, *6:* 48
Animal experimentation
see also Biologic assay; Pharmacologic research; Toxicology
health hazards for man in, *8:* 3
see also under Personnel
improvement of techniques and handling of animals in, *8:* 6
legal aspects of, *6:* 63
licensing, Gt. Britain, *6:* 47
mortality of animals from exposure vs. environment, *2:* 299
reaction of animals to gentling and handling, and, *7:* 94
selection of animals, *5:* 102
design of, and, *6:* 23
selection of normal animals for, by electrophoresis of serum proteins, *1:* 323
use of animals in, *see under* specific kind and groups of animals and type of research
variance in,
environmental control, and, *6:* 37
see also under Temperature
Animal technician, *see* Personnel
Animal Technicians Association, *8:* 4, 16
publication by, *9:* 16
Animals (general)
see also Breeding; Diets; Diseases; Domestic animals; Handling; Housing; Laboratory animals; Restraint; for comparative data *see* Mammals
anatomic, physiologic, genetic relations
effects of temperature on, *1:* 146
behavior patterns
neurological basis of, *1:* 3
population, vs., *1:* 107
wild, of; effects of captivity and environment on, *1:* 85
biological data on, *1:* 256
blood
hematology, *2:* 47, 83
respiratory functions of, *1:* 42
standard values in, *1:* 114
blood types, review, *2:* 353
body
size and temperature relationship, *1:* 146
temperature, *2:* 83
bone marrow, standard values in, *1:* 114
books, pamphlets, etc., on, *see* Books and pamphlets; Bibliographies; Conferences and Symposia; Films
circulatory system, *1:* 486
endocrinology, *1:* 159
enzymes, liver; body size, species variation in activity, *1:* 221
eyes
anatomy and physiology, *1:* 260
retinal circulation, *1:* 192
genetics, *1:* 256
hair growth, *1:* 171
immunity, resistance to disease; species, individual variation, *6:* 30
immunology, *2:* 114
metabolism, standard values, *3:* 35
nervous system, *1:* 3
nutrition, *3:* 18, 35, 40
physiology, *1:* 115, 316
reproductive, *1:* 393
reproduction, *1:* 316
see also under Breeding
pregnancy
effects on blood, *1:* 12
effects on circulation, *1:* 486
sexual activity, effects of light on, *1:* 19
respiration, tissue respiration, *1:* 42, 394
Animation, suspended, *1:* 396
Anthropoids
see also Baboon; Monkey
body, organ, gland weights, *1:* 37
Antibiotics
see also Chlortetracycline; Griseofulvin; Penicillin, etc.
as dietary additives, *see under* Dietary additives
effect on tumor transmission in chicken, *2:* 356
toxicity
for guinea pig, *2:* 153
for laboratory animals, *2:* 347
treatment of diseases, in, *2:* 42, 67, 119, 153, 154, 166, 190, 227, 269, 275, 280; *3:* 17; *7:* 115
Anticruelty laws, *see* Humane treatment
Antigen testing, use of mouse in; techniques, *1:* 229
Antivivisection, *see* Humane treatment
Appendectomy, effects on rabbit, *2:* 93
Aramite in control of parasites, *2:* 64, 318, 320
Architectural plans for animal houses, *see* "construction design" *under* Housing
Argonne National Laboratory animal facilities, *5:* 115
Armadillo, reproduction; use in genetics research, *1:* 511
Arterial constriction device for rat, *7:* 183
Arteriosclerosis research, use of animals in, *1:* 418; *4:* 74
Arthritis research, use of swine in, *2:* 253
Artificial insemination, *see under* Breeding
Artificial respiration equipment
for animals, *7:* 149
for cow and horse, *7:* 131

Artificial respiration equipment (*continued*)
for dog, *7:* 130
for rat, *7:* 118
Ascaridae, *2:* 362
Aspicularis tetraptera, *2:* 190
Atherosclerosis research
use of animals, birds in, *1:* 285; *2:* 196, 306; *6:* 53
Atmospheric pressure, effects of, *see* Altitude
Atrial pressure measurement, in dog, *7:* 47
Aureomycin, *see* Chlortetracycline

Baboon
see also Animals; Monkey
fat deposition in; use for atherosclerosis research, *2:* 196
Bacillus anthracis, *3:* 80
Bacillus piliformis, *2:* 266
Bacillus stearothermophilus, *5:* 111
Bacillus subtilis, *2:* 117
Bacteria, airborne transmission of, *2:* 117
Bacterial disease research; bacteriologic research, *see* Microbiologic research; for diseases in animals, *see* "bacterial" *under* Diseases
Bacteriology, book, *2:* 114
Bacterium bronchisepticum, *2:* 41
Bandaging method for skin grafts in mouse, *7:* 74
Barbiturates, *see under* Anesthesia
Bartonella bacilliformis, *2:* 231, 289
Bartonella muris, *2:* 311
Basenjis, *1:* 96, 363
Bat
see also Diseases
blood electrolytes, *1:* 317, 398
body, organ, gland weights, *1:* 37
weight and metabolic rate in pregnancy and at birth, *1:* 259
eyes, anatomy and physiology, *1:* 26
rabies infection carrier, as, *2:* 295
Beagle, *1:* 76, 96, 103, 324, 363; *2:* 194, 234, 355; *4:* 100
Bedding materials for laboratory animals, *5:* 28, 75, 117, 123
see also under Housing
Behavior in animals, *see under* specific kind or groups of animals
Behavior pattern measurement techniques, *1:* 3
activity measuring device, *7:* 188
chamber for mouse, *7:* 179
drive in cat, ergometer for, *7:* 163
effect of deficient diet, *7:* 156
effect of drugs on inbred mouse, *1:* 407
effect of tranquilizers on small animals, *7:* 143, 155
emotional defecation in rat, *1:* 158
food-sharing tests in young monkey, apparatus for, *7:* 173
induction of changes in cat, mouse, rat, *7:* 191
in monkeys, *1:* 399; *7:* 155, 188
in rat, *1:* 87, 158; *7:* 155, 191
Behavior research, use of animals in, *1:* 444; *6:* 28
Bibliographies
Animal Breeding Abstracts, *9:* 2
Avian Mycosis, *2:* 140
Behavior Studies on Inbred Mice, *1:* 407
Bibliography of Agriculture, *9:* 3
Bibliographia Primatologica, *1:* 43
Biological Abstracts, *9:* 4
care of guinea pig in clinical research and sources of supply, *5:* 125
Coccidiosis, *2:* 55
Diseases in Wild Mammals and Birds, *2:* 81
dog, *1:* 481
Effects of Cold on Man, *1:* 440
ICLA Bulletin, *9:* 11
Information on Laboratory Animals for Research, *9:* 13
Primate Malaria, *2:* 14
Rabbit as Used in Disease Research, *2:* 9
rabbits, *1:* 254
Radioisotopes in Animal Physiology, *7:* 140
rats, feed and equipment for, *5:* 12
Veterinary Bulletin, *9:* 21
Bile collection techniques
for cat, *6:* 18
for dog, rat, *7:* 175
Biological assay and research
see also Animal experimentation
production of inbred mice and rats for, *4:* 47
use of germfree animals in, *4:* 112
use of mouse in, *6:* 4
Biological environment, physiologic and psychologic effects of, *see under* Handling; Human contact; Population dynamics; for pathologic effects, *see* "bacterial," "fungal," *etc.*, *under* Diseases
Biontology, definition of, *1:* 468
Birds
see also Breeding; Chicken; Diets; Diseases; Duck; Housing; Pigeon; Poultry; Turkey
anatomy, *1:* 48, 135
behavior patterns, *1:* 185
body, organ, gland weights, *1:* 37
books, bibliographies on:
Avian Anatomy, *1:* 48
Bibliography of Avian Mycosis, *2:* 140
Bibliography of References to Diseases in Wild Mammals and Birds, *2:* 81
Diseases in Captive Wild Mammals and Birds, *2:* 2
carotid body and sinus, anatomy, macro- and microscopic; embryology and physiology, *1:* 322
circulatory system, *1:* 486
eyes, anatomy and physiology, *1:* 260
hematology, *1:* 12, 71, 135
longevity of wild, *2:* 81
nutrition of wild, *2:* 81
physiology, *1:* 135
environmental, *1:* 185
reproductive, *1:* 185, 393
wild, of, *2:* 81
spermatogenesis and gonads of white-crowned sparrow, effects of light on, *1:* 9
Bleeding, effects of, *see* Blood loss
Bleeding techniques, *1:* 229
see also Blood collection techniques
Bleeding volume recording in dog, *7:* 67
Blindness, effect on inbred mouse, *1:* 182
Blood analysis, *see under* Blood study techniques
Blood circulation study technique, in rabbit, *7:* 152
Blood collection techniques
birds, *1:* 12
holder for, *7:* 5
catheterization, intra-arterial, and sampling from, *7:* 41
cattle, *1:* 12; *7:* 31
chick embryo, *7:* 51
chicken, *7:* 126
dog, *7:* 67
cannulating device for, *1:* 131
catheterization of major vessels, *1:* 184; *7:* 186
ferrets, *1:* 39
guinea pig, *7:* 34
hamster, *1:* 67
horse, *1:* 12
laboratory animals, *1:* 12, 71, 135, 403; *7:* 160
monkey, *5:* 96
mouse
arterial and venous, of embryo and newborn, *7:* 30
from jugular vein of weanling and adult, *7:* 57
in newborn, *7:* 127
rabbit, vacutainer device for, *7:* 76
rat, *7:* 34
newborn, *7:* 127
sheep, *7:* 31, 145

Blood collection techniques (*continued*)
storage, and, *7:* 180
swine, *1:* 12; *7:* 31
Blood flow measurement techniques
dog, *1:* 250
bronchial, *1:* 435
coronary, *7:* 52
venous occlusion plethysmography, *1:* 248
in liver of various animals, with radio-iodine, *1:* 279
rat, in mesoappendix, *7:* 54
Blood loss
effect on dog, *1:* 214, 367
effect on monkey, *2:* 175, 338
effect on rabbit, *1:* 242
Blood pressure
see also under specific kind of animal
device for producing hypertension in rat, *7:* 183
measurement techniques for
cat, arterial, cannulation device for, *7:* 158
cattle, *1:* 368
arterial, *7:* 132
dog, *1:* 368; *7:* 87
arterial, *7:* 132
and venous, in paw, *1:* 442
by tail plethysmograph, *7:* 22
guinea pig, *1:* 255
hamster, *1:* 201, 433
horse, *1:* 368
arterial, *7:* 132
mouse, membrane, manometer system, *7:* 63
rabbit
ear arteries and veins, *1:* 441
systolic, *7:* 8
rat, *1:* 225, 130, 145, 268; *7:* 26
arterial, by tail plethysmograph, *7:* 22
swine, *1:* 368
Blood study techniques
see also "blood," *under* specific kind of animal
cellular and chemical, review, *7:* 81
coagulation time determination, *2:* 145; *7:* 19
counts, short cuts for, *7:* 180
eosinophil count, stains for, *7:* 119
erythrocyte, life span, with radioisotopes, *1:* 50, 122, 447
volume, *1:* 488
hematocrits
circulating and tissue, with radioisotopes, *1:* 450
method, for blood cell volume, *1:* 354
hemoglobin, by electrophoresis, *1:* 218, 400, 415
hormones, thyrotropic and gonadotropic, determination, *1:* 261
leukocytes, cytology, staining, techniques, *1:* 98
pH measurement, *1:* 513
phagocytic activity of reticuloendothelial system, with radio-iodine, *1:* 279
plasma
available fluid volume, and, *1:* 34
red cell volume, and, with radioisotopes, *1:* 294
volume, with radioisotopes, *2:* 307
proteins
by electrophoresis, *1:* 299, 451, 506, 512; *2:* 98, 145, 313
for rabies test, *2:* 76
for selection of experimental rabbits, diagnosis of disease, *1:* 323; *2:* 313
urea determination, *7:* 146
volume
dyes and radioisiotpes, *1:* 222, 437
pulmonary, with radioisotopes, *1:* 108, 478
with radioisotopes, *2:* 307
Blood substitutes, tolerance of cat for Periston, *2:* 63
Blood transfusions
in cat, and tolerance for, *2:* 63
in dog, *1:* 397
effect on plasma volume and proteins, *1:* 374
in laboratory animals, *7:* 81
in rabbit and rat; perfusion pump for cross transfusion, *7:* 124
in small animals; equipment for cross transfusion, *7:* 184
Blood vessels
see also under specific kind and groups of animals
cholesterol biosynthesis *in vitro*; species variation, *1:* 326
morphologic classifications, electron microscopy for, *1:* 423
study techniques; counting in rat, *1:* 300
by intra-arterial injection in rabbit ear, *7:* 42
use of hamster in study of, *6:* 29
Body defense mechanism research, use of germfree animals in, *6:* 55
Body fluid studies and techniques, review, *7:* 81
Body measurement, models and formulas for, *7:* 93
Body temperature measurement in
see also "body temperature" *under* specific kind and groups of animals
cattle; rectal, skin, hair, *1:* 379
dog, *1:* 344
mouse, and equipment for, *2:* 155
rabbit; rectal, skin, hair, *1:* 379
rat, subcutaneous, *7:* 53
Body volume measurement in guinea pig, by air displacement, *7:* 138
Body water measurement in
see also "body water" *under* specific kind and groups of animals
cat, *1:* 95
mouse, *1:* 211
rat, *1:* 211
Bone drilling device for intracerebral injections in monkey, *7:* 65
Bone marrow collection
see also "bone marrow" *under* specific kind and groups of animals
cat, *1:* 74
dog, *1:* 54, 74, 153
rat, *1:* 75
study techniques
apparatus for sketching from slides, *1:* 55
chemical analysis, *1:* 63
erythrocyte life span, with radioiron, *1:* 447
nucleated cell counts and cellular distribution, *1:* 432
volume estimation, *1:* 55
Books and pamphlets
see also Bibliographies; Conferences and symposia; Films
Airborne Contagion and Air Hygiene, *5:* 83
Allergy, *2: 19*
Anatomical and Physiological Studies on the Growth of the Inner Ear of the Albino Rat, *1:* 1
Anatomy of the Cat, *1: 18*
Anatomy of the Gorilla, *1:* 88
Anatomy of the Rabbit, Practical, *1:* 81
Anatomy of the Rabbit, a Laboratory Guide to the, *1:* 94
Anatomy of the Rat, *1:* 453
Anatomy of the Rhesus Monkey, *1:* 13
Animal Colony Maintenance, *5:* 19
Animal Diseases, *2:* 123
Animal Nutrition, *3:* 40
Animal Pathology, *2:* 72
Animal Physiology, Handbook of, *1:* 316
Animals for Research, a Catalog of Commercial Sources, *6:* 45
Animaux de Laboratoire: Anatomie, Particularités physiologiques, Hématologie, Maladies naturelles, *1:* 135
Annotated Catalogue of Mutant Genes of the House Mouse, *1:* 245
Approved Laboratory Technic, *1:* 101
Association of American Feed Control Officials, Official Publication of the, *3:* 37
Avian Anatomy, Atlas of, *1:* 48
Basic Care of Experimental Animals, *5:* 1
Biological Data, Handbook of, *1:* 256
Biology of the Laboratory Mouse, *1:* 44
Blutmorphologie der Laboratoriumstiere, *1:* 403
Breeding and Care of Albino Rat for Research Purposes, *4:* 2
Canine Medicine, *2:* 330
Canine Surgery, *2:* 178

Books and pamphlets (*continued*)
Care and Breeding of Laboratory Animals, 5: 27
Care of the Dog Used in Medical Research, 5: 24
Care and Feeding of Laboratory Animals, 5: 57
Care of Laboratory Animals, 5: 75
Care of Laboratory Animals, Practical Guide on the, 5: 117
Care and Management of Laboratory Animals, 5: 123
Care of a Small Rat Colony, 5: 12
Cat Anatomy, Atlas of, 1: 46
Cat Care, the Complete Book of, 1: 162
Cell, Biochemistry, Physiology, Morphology, 1: 427
Circulation, Handbook of, 1: 486
Communicable Diseases of Laboratory Animals, Notes on, 2: 27
Comparative Anatomy of the Nervous System of Vertebrates Including Man, 1: 21
Comparative Animal Physiology, 1: 115
Comparative Morphology of Carotid Body and Carotid Sinus, 1: 322
Comparative Physiology of Respiratory Mechanisms, 1: 42
Culture Methods for Invertebrate Animals, 4: 4
Development of Vertebrates, 1: 267
Diagnosis of Parasites in Animals, 2: 6
Diagnosis and Therapy, Reference Handbook for the Veterinarian, 2: 83
Disease in Captive Wild Mammals and Birds, 2: 2
Diseases of Laboratory Primates, 2: 360
Diseases of Poultry, 2: 298
Diseases of Swine, 2: 219
Diseases Transmitted from Animals to Man, 2: 82
Dissection of the Cat, 1: 247
Dissection of the Dog, Guide to the, 1: 113
Dissection of the Rabbit, with an Appendix on the Rat, 1: 266
Domestic Rabbit Production, 4: 58
Embryology of the Opossum, 1: 30
Energy Requirements of Beef Calves for Maintenance and Growth, 3: 32
Environmental Physiology of Farm Mammals, 1: 178
Establishment and Maintenance of a Disease-free Animal Colony, 4: 82
Exposure Chambers for Research in Animal Inhalation, 7: 193
Experimental Surgery, 7: 172
Feed Required to Produce 6-Pound Rabbits after Weaning, 3: 15
Feeds and Feeding, a Handbook for the Student and Stockman, 3: 18
4-H Rabbit Raising Handbook, 5: 110
Frog, Its Reproduction and Development, 4: 20
Functional Anatomy of the Mammal, 1: 112
Functional Anatomy of the Rabbit, Principles of, 1: 62
Fungal Diseases of Animals, 2: 291
Genesis of the Rat Skeleton, 1: 321
Genetics of the Dog, 4: 24
Genetics of the Mouse, 1: 110
Geschwülste der Laboratoriumsnagetiere, 2: 221
Guinea Pig in Research: Biology, Nutrition, Physiology, 3: 74
Haltung und Zucht von Versuchstieren, 5: 81
Humane Experimental Technique, the Principles of, 8: 16
Immunology and Serology, 1: 229
Index of Diagnosis (Clinical and Radiological) for the Canine and Feline Surgeon, 2: 54
Index of Treatment in Small-Animal Practice, 2: 69
Laboratory Animals, Handbook of, 4: 45
Lehrbuch der vergleichenden Anatomie der Haustiere, 1: 355
Life Processes in Gray Norway Rats During 14 Years in Captivity, 1: 35
Life Processes and Size of the Body and Organs of the Gray Norway Rat During 10 Generations in Captivity, 1: 7
Mammary Tumors in Mice, 2: 16
Medical and Public Health Laboratory Methods, 7: 81
Microscopic Anatomy of the Digestive System of the Chicken, 1: 170
Morphologische, Biologische und Serologische Eigenschaften der Bartonellen, 2: 289
Neoplasms of the Dog, 2: 25
Neoplasms of the Domesticated Mammals, 2: 88
Neurologic Examination of the Dog with Clinicopathologic Observations, 2: 113
Neurological Foundations of Animal Behavior, 1: 3
Nutrition of the Dog, 3: 16
Osteology of the Reptiles, 1: 257
Pathologie der Laboratoriumstiere, 2: 207
Patterns of Mammalian Reproduction, 1: 61
Pharmacology, 7: 164
Phosphate Fertilization of Alfalfa and Some Effects on Animal Physiology, 3: 52
Physiology of Domestic Animals, 1: 27
Physio-Pathologie de la Reproduction et Insemination Artificielle des Animaux Domestiques, 1: 353
Pigeon, 1: 311
Planning Your Animal Hospital, 5: 25
Possums, 1: 111
Praktische Tierpflege für Naturfreunde und Forscher, 5: 46
Primate Thalamus, 1: 33
Progress in the Physiology of Farm Animals, 1: 185, 457
Psychological Research on the Rat, Handbook of, 1: 87
Rabbit, 1: 263
Rabbit and Cat Diseases, 2: 1
Rabbits' Ailments; a Short Treatise on the Domestic Rabbit in Health and Disease, 2: 135
Raising Hamsters for Science, 4: 10
Raising Rabbits, 4: 115
Rat; Data and Reference Tables for the Albino Rat and Norway Rat, 1: 2
Rat in Laboratory Investigation, 1: 45
Reproduction in Domestic Animals, 1: 438
Reproduction in the Rabbit, 1: 4
Reproductive Physiology, 1: 393
Respiration, Handbook of, 1: 394
Restraint of Animals, 7: 33
Retinal Circulation in Man and Animals, 1: 192
Richtlinien für die Sektion der Haustiere, 7: 100
Salmonellosis in Animals, 2: 137
Skeletal Development of the Rat; Atlas of the, 1: 121
Spine of the Dog, Experimental and Clinical Studies of, 1: 20
Standard Values in Blood, 1: 114
Standard Values in Nutrition and Metabolism, 3: 35
Theory and Practice of Nutria Ranching, 5: 118
Topographical Anatomy of the Dog, 1: 428
Toxicology, Handbook of, 2: 347
Tumeurs Spontanées des Animaux de Laboratoire: Souris, Rat, Poule, 2: 65
U.F.A.W. Handbook on Care and Management of Laboratory Animals, 5: 102
Veterinary Annual, 2: 353
Veterinary Bacteriology and Virology, 2: 114
Veterinary Clinical Parasitology, 2: 75
Veterinary Clinical Pathology, Manual of, 2: 47
Veterinary Drug Encyclopedia and Therapeutic Index, 2: 279
Veterinary Endocrinology, a Handbook of, 1: 159
Veterinary Helminthology and Entomology, Mönnig's, 2: 112
Veterinary Necropsy Procedures, 2: 68
Veterinary Ophthalmology, 1: 260
Veterinary Pathology, 2: 185
Veterinary Pharmacology and Therapeutics, 2: 172
Veterinary Toxicology, 2: 162
Viruses, 2: 301
Wild Animals in Captivity, 1: 85
Boxer, *2:* 96
Breeders and dealers of laboratory animals, commercial
animal maintenance, viewpoint of, *5:* 19
care and housing of animals, guide lines for, *5:* 28
catalog of, *6:* 58
inbred mice; accreditation, certification, standards, specifications, *4:* 65
random bred, and; accreditation, standards, *4:* 76
inbred and random bred rats; standards, *4:* 109
methods for cost considerations, *8:* 1
organization, activities, *6:* 57
of rabbits and cavies; rules and unfair trade practices, *6:* 50
responsibilities of, *6:* 63
sales problems, records, *6:* 44

Breeding
see also Genetics; Hormones; *see also* "genetics," "reproduction and sex organs" *under* specific kind and groups of animals
amphibia, *5:* 27
animals, including laboratory animals
administration of colony, *4:* 50
bacteriological screening, standard operating procedure, *5:* 123
books, bibliographies, conferences, reviews, symposia, *4:* 8, 51, 62, 112; *5:* 1, 19, 27, 46, 57, 81, 102, 123; *9:* 2, 6, 16
cesarean section for disease-free, *4:* 82
closed and open, random and inbred, *4:* 73
closed colony, advantages of, *4:* 40
controlled, mating techniques, *4:* 8
costs, *8:* 9
capital and operating, *8:* 7
equipment for, *4:* 38
factors affecting, *4:* 62
genetics, *4:* 64
and variances, *4:* 73
housing, *5:* 72
cages and equipment, *4:* 38
air conditioning, sanitation, for disease-, pathogen-free, *4:* 87; *5:* 129
isolator, for germfree, *4:* 99
plastic, sanitation, germicides for germfree, *4:* 114
management of, and, *5:* 17, 18, 123
space requirements, *5:* 63
inbreeding; genetic control, mating, *4:* 37
selection of animals, *4:* 9
selective breeding, and; selection of stock, *4:* 25
value of controlled pure strains, *4:* 34
vs. random breeding, *4:* 53, 73
mating and mating techniques, *4:* 8; *5:* 19
cycle determination method, *4:* 1
monogamous, polygamous; breeding data; pregnancy tests, *5:* 123
methods for production of, disease-free, *4:* 105
mortality, neo- and postnatal; rearing of young, *4:* 56
radiobiologic research, for, *5:* 21
random breeding; selection, breeder rotation, *4:* 1
selection of animals, diet, environment, for disease-free, *4:* 70
methods, *4:* 1; *6:* 23
space and production estimates, *5:* 123; *see also* "housing" *above*
standards for, *6:* 19
surgical procedure and management of germ- or pathogen-free, *4:* 102
artificial insemination, physiopathology of, *1:* 353
see also under "cat," "dog," "domestic animals," "guinea pig," "mouse," "rabbit," "sheep"
review, *2:* 353
birds, caged
see also "chicken," "domestic animals," "poultry"
sexing of, *2:* 198
cat, *4:* 98; *5:* 27, 34, 38, 57
see also "animals," "domestic animals"
artificial insemination, *1:* 353
breeding age; estrus, gestation periods, *5:* 117
controlled; mating techniques, *4:* 8
housing and care; diets for young, *4:* 27
inbreeding; mating, genetic control, *4:* 37
mating and mating techniques, *4:* 8, 84
behavior of female, *1:* 390
mortality, prenatal, *4:* 55
use of hormones, *4:* 84
chicken, *4:* 23; *5:* 57
see also "animals," "domestic animals," "poultry"
design and operation of Reyniers System for germfree, *4:* 113
disease control, and, *2:* 99
chinchilla, diets for, *3:* 51
dog, *5:* 27, 57
see also "animals," "domestic animals"
artificial insemination, *1:* 353; *4:* 15
collection, preservation, transportation of semen, *4:* 63, 106
breeding age; estrus, gestation period, *5:* 117
control of disease, and; vaccination, *4:* 42
of parasites, *2:* 26
controlled, *4:* 8
cross breeding, bull terrier with Dalmatian, *4:* 28
delivery of young, *4:* 14
diets for, *3:* 51; *4:* 100
hand-feeding of newborn, *4:* 87
housing for, *4:* 100
inbreeding; mating, genetic control, *4:* 37
litter size, mortality in newborn Airedale, foxhound; effect of temperature, diet on, *4:* 41
mating and mating techniques, *4:* 8, 15
methods, *4:* 24
rearing newborn in absence of bitch, *4:* 80
domestic animals, *4:* 54
see also "animals," "cat," "cattle," "chicken," "dog," "horse," "poultry," "rabbit," "sheep," "swine"
artificial insemination, *1:* 353, 438
mating, gestation, lactation; effect of light on, *4:* 46
Drosophila, *5:* 27
ferret, *1:* 39; *4:* 66; *5:* 27
artificial light, in, *4:* 66
control of parasites, and, *4:* 42
fish, *5:* 27
fox, mating, controlled breeding, *4:* 8
guinea pig, *5:* 27, 57
see also "animals"
artificial insemination, collection of semen, *4:* 86
intraperitoneal; comparative results, *4:* 97
breeding age; estrus, gestation period, *5:* 117
control of disease, and; vaccination, *4:* 42
controlled, mating techniques, *4:* 8
costs, *8:* 12
hand-feeding of newborn, *4:* 87
housing, *5:* 78
design and operation, of Miyakawa unit for germfree, *4:* 108
of Reyniers System for germfree, *4:* 113
space requirements, *5:* 63
inbreeding; mating, genetic control, *4:* 37
litter size, mortality, *4:* 12
mating and mating techniques, *4:* 8
colony, standard operating procedures, *5:* 123
monogamous, *4:* 12
standard operating procedures, *5:* 123
time of, effect of diet on, *3:* 57
methods for germfree, *4:* 111
mortality, in closed unit, *4:* 39
prenatal, *4:* 55
hamster, *4:* 10; *5:* 27, 57
see also "animals"
breeding age; estrus, gestation period, *5:* 117
Chinese, *4:* 81
controlled, *4:* 8
costs, capital and operating; diets, *4:* 83
housing, cages; temperature, *4:* 5, 7
space requirements, *4:* 83
inbreeding, of golden; effect on weight, *4:* 60
mating, genetic control, *4:* 37
mating and mating techniques, *4:* 8, 37
age, gestation period, handling, *4:* 5, 7
and litter size, number, weaning, *4:* 3, 5, 7
time of, and environmental conditions, *4:* 7
salmonellosis epidemics, and, *2:* 108
horse, controlled
see also "animals," "domestic animals"
mating techniques, *4:* 8
monkey, *5:* 27, 57

Breeding (*continued*)
see also "animals"
breeding age; estrus, gestation period, *5:* 117
controlled, mating techniques, *4:* 8
mouse, *5:* 27, 43, 57
see also "animals"
artificial insemination of inbred, results, *4:* 48
breeding age: estrus, gestation period, *5:* 117
cesarean section for pathogen-free, *4:* 87
closed, for Salmonella infection-free, *2:* 274
commercial; housing, care, management, *8:* 1
controlled, *4:* 8
costs, *5:* 109; *8:* 1, 12
capital and operating, of inbred, *4:* 83
diets for, *3:* 14, 51; *4:* 83
autoclaved stock, *4:* 31
testing of adequacy of, *4:* 11
disease
control, *2:* 23, 122, 254, 327; *4:* 26, 76
incidence, *2:* 20, 21, 254, 259, 264
vaccination, *2:* 118; *4:* 42
grouping; litter size, weaning, *4:* 6
hand-rearing of cesarean-born germfree by forced feeding; results, *3:* 85
housing, cage, *5:* 54
cage population and estrus, *4:* 116
commercial colony, in, and costs, *8:* 1
design and operation of Reyniers System for germfree, *4:* 113
equipment, sanitation, temperature, *4:* 13
maintenance of disease-free, and, *4:* 82; *5:* 109
space requirements, *4:* 83; *5:* 63
inbreeding; costs, diets, space requirements, *4:* 83
genetics, standards; methods of raising, *4:* 65
and variances, *1:* 213
maternal age, selection, fertility, statistics, *4:* 103
mating, genetic control, *4:* 37
pregnancies, litter size; effect of hormones on, *4:* 75
methods; hybridization and selection, *4:* 57
pregnancy incidence after coitus, strain variation, *4:* 17
recording, *4:* 59, 76
selection for audiogenic susceptibility, *4:* 36
standards, *4:* 65, 76
and tumor incidence in, *4:* 101
maternal age, *1:* 410; *4:* 103
mating and mating techniques, *4:* 8, 37, 75; *8:* 1
colony, standard operating procedure, *5:* 123
for large scale production, *4:* 43
monogamous, *4:* 11
and polygamous, standard operating procedure, *5:* 123
seasonal rhythm of fertility in albino and fawn, *4:* 47
time of, modification by external stimuli associated with male, *4:* 67
mortality in closed unit, *4:* 39
prenatal, *4:* 55
postnatal, and; effect of temperature on, *1:* 330
outbreeding; selection for audiogenic susceptibility, *4:* 36
random, records, standards, *4:* 76
replacement of colony, commercial, *8:* 1
selection, management, *4:* 26
use of hormones and neonatal losses, *4:* 75
in vitro, *4:* 94
opossum, *1:* 160; *5:* 27
care and management, *5:* 128
controlled breeding; mating, *4:* 8
pig, miniature, *4:* 35, 61; *see also* "swine"
pigeon, *1:* 311; *see also* "birds"
poultry, *5:* 27; *see also* "birds," "chicken," "domestic animals"
rabbit, *4:* 58, 115; *5:* 27, 57, 110
see also "animals," "domestic animals"
artificial insemination, *1:* 353
conception, litter size vs. interval of sperm ejaculated, *4:* 88
intraperitoneal technique, *4:* 89
mixed semen; effect on weight of offspring, *1:* 227
pH of diluted stored semen and fertilizing capacity; sex of offspring, *4:* 92
breeding age; estrus, gestation period, *5:* 117
cesarean delivery for germfree, *4:* 117
coccidiosis prevention, and, control, *4:* 69, 93
controlled, *4:* 8
costs, *8:* 12
diets, and, *3:* 51; *4:* 33, 69
for young germfree, *4:* 117
failures due to soybean forage, *3:* 71
genetic factors in, *4:* 21
hand-rearing of cesarean-born by forced feeding, results, *3:* 85
housing, cages, nest box, *4:* 79
maintenance of disease-free, *4:* 82
sanitation, *4:* 69
space requirements, *5:* 63
inbreeding; genetic control, *4:* 37
mating and mating techniques, *4:* 8, 37
mortality in bucks, does, young, and, *4:* 18
prenatal, *4:* 55
pregnancy determination, standard operating procedure, *5:* 123
standard operating procedure, *5:* 123
weaning of young; effect of time on weight gain and rebreeding, *4:* 107
rat, *1:* 151; *4:* 2; *5:* 27, 57
see also "animals"
breeding age; estrus, gestation period, *5:* 117
cannibalism in, and; effect of diet on, *4:* 90
cesarean section, for pathogen-free, *4:* 19, 87
quarantine, *4:* 19
Reyniers germfree technique, *4:* 78
controlled, *4:* 8
copulation determination, equipment, *4:* 38
diet, and, *3:* 14, 51; *4:* 16, 22
autoclaved, *4:* 31
effect
on litter size, *4:* 91
on mating performance, *4:* 22
on ringtail in infants, *2:* 216
for germfree, *4:* 104
for inbred, *4:* 83
for pathogen-free, *4:* 68
diseases, and control, *2:* 254
diagnosis, *4:* 68, 96
ringtail in infants, control, *2:* 216, 281; *4:* 77
ringworm; effect of practices on, *2:* 309
hand-rearing of cesarean-born germfree by forced feeding; results, *3:* 85
housing
cages, *5:* 54
care, and, *4:* 2
environmental control, sanitation, for pathogen-free, *4:* 49, 68, 85
design and operation
of Reyniers System for germfree, *4:* 113
of stainless steel system for germfree, *4:* 104
humidity requirements and ringtail in infants, *4:* 77
maintenance of disease-free, and, *4:* 82; *5:* 109
space requirements, *5:* 63
inbreeding
costs, diet, space requirements, *4:* 83
mating, genetic control, *4:* 37
seasonal rhythm of fertility, *4:* 47
standards, *4:* 109
lactation, prolongation of, by litter replacement, *4:* 110
lighting, artificial, and, *4:* 16
effect on litters, *4:* 32
effect on mating performance, *4:* 22
littermate and nonlittermate colonies; costs, *4:* 52

Breeding (*continued*)
mating and mating techniques, *4:* 8, 37
colony, standard operating procedure, *5:* 123
effect of early experience, *4:* 30
monogamous and polygamous, standard operating procedure, *5:* 123
performance; effect of diet and light on, *4:* 22
rearing, and, *5:* 12
sex ratio; effect on litter size, *4:* 91
method and practices for pathogen-free, *4:* 72, 96
mortality, prenatal, *4:* 55
random, standards, *4:* 109
selection; progeny testing in prevention of lung disease, *4:* 29
sexual maturity; effect of light on, *1:* 41
split-litter techniques, *1:* 87
wild, *5:* 106
reptiles, *5:* 27
sheep
see also "animals," "domestic animals"
artificial insemination, intraperitoneal, *4:* 97
effect of mixed semen on weight of offspring, *1:* 227
swine
see also "animals," "domestic animals," "pig, miniature"
dietary requirements, and, *3:* 36
method for disease-free, *4:* 118
mortality, prenatal, *4:* 55
British Veterinary Codex, *1:* 260
Brookhaven animal colony, *5:* 45
Brucella bronchiseptica, *2:* 288
Brucella intermedia, *2:* 182
Brucella suis, *2:* 117
Business management, *see* Administration; Costs; Records
Butyl cinnamate, in treatment of disease, *2:* 85

Cadmium anthranilate, in treatment of disease, *2:* 190
Cages for
see also Activity cages; Metabolism cages; Restraint and protective devices and techniques; "housing" *under* Breeding; for feeding, watering devices on, *see* Feeding devices; Watering devices
animals (laboratory), *5:* 4, 52, 85, 90, 117
battery vs. unit system, size, capacity, *5:* 132
bedding for, and, *5:* 75
capacity, *5:* 75
space for, and, *5:* 123
cleaning, sterilization, *5:* 18, 75
construction design, racks, *5:* 77
costs, *5:* 30
disease-free, for, *4:* 87; *5:* 129
disinfestation with chlordane, etc., *2:* 268
glass, for small, *5:* 5
isolating compartments in, *5:* 4
isolation, *2:* 32; *5:* 54, 116
construction and arrangement of, *5:* 17
for germfree, *4:* 99
number of, per, *5:* 30, 39, 123
plastic, capacity, *5:* 39
and steel, specifications for, *5:* 59
racks for, *5:* 62, 77
sanitation standards for, *5:* 30
size, *5:* 21, 30, 75, 129
ventilation, *5:* 75
cat, *5:* 4
chicken, germfree, *3:* 83
dog, *3:* 17; *4:* 14; *5:* 4, 50
convalescent, combination, storage, *5:* 50
and storage, *5:* 26
size, *5:* 21
and cost, *5:* 30
guinea pig, *5:* 97
automatic flushing mechanism, with, *5:* 120; *see also* "rodents"
battery vs. unit system; size, capacity, *5:* 132
for maintenance and breeding; capacity, bedding, *5:* 28
number of, per, *5:* 28, 30
size, *5:* 21
and cost, *5:* 30
hamster, *4:* 5
isolation, disposable, *5:* 116
metal, *4:* 7
monkey, *5:* 4
and arrangement with automatic water system, *5:* 134
isolation, *2:* 32
mouse, *5:* 114
arrangement of, *5:* 113
battery vs. unit system; capacity, size, *5:* 132
carrying, *5:* 54
construction materials and design; size, cleaning, *5:* 37
glass, adjustable, *5:* 13
for inbred and random bred, *4:* 76
isolation, *5:* 54, 116
maintenance and breeding, *5:* 54
and bedding, *5:* 28
and experimental use, *5:* 9
number of, per, *5:* 28, 30; *8:* 1
plastic, disposable, *5:* 131
vs. metal; effect on tumor incidence, *5:* 80
for radioisotope research, *5:* 54
with runway, space requirement, *5:* 15
sanitation for control of epidemics, *2:* 122
size, *4:* 6; *5:* 21
and cost, *5:* 30
rabbit, *5:* 4
automatic flushing device, *5:* 120
maintenance and breeding, bedding, *5:* 28
nest box, *4:* 79
number of, per, *5:* 28, 30
size, *5:* 21
and cost, *5:* 30
radiobiologic research, for, *5:* 21, 33, 47, 54, 124
rat, *4:* 2
battery vs. unit system; size, capacity, *5:* 132
carrying, *5:* 54
cleaning; device for lifting rats, *5:* 20
construction material and design; size, cleaning, *5:* 37
glass, *5:* 6
isolation, *5:* 54, 116
maintenance and breeding, *5:* 54
and bedding, *5:* 28
and experimental use, *5:* 9
number of, per, *5:* 28, 30
size, *5:* 21
and cost, *5:* 30
recommendation for optimum, *5:* 91
standards for random and inbred, *4:* 109
steel, and ringtail incidence, *2:* 319
rodents, disposable isolation, *5:* 116
special, design, *5:* 41; *see also* Activity cages; Metabolism cages
squirrel, *5:* 14
Caging, effect of crowding, isolation, *see under* Population dynamics
Callosciurus, *1:* 472
Caloric requirement measurement techniques, *see* Energy requirement
Canary, *1:* 71; *2:* 27
Cancer chemotherapy and cancer research
for cancer in animals, *see* "tumors" *under* Diseases
cage, restriction, for mice, *5:* 33
implantation techniques, *2:* 107, 333; *7:* 114
tissue culture chamber for phase microscopy, *7:* 190
use
of animals in; genetic control, *4:* 37
of inbred mouse in, *4:* 65
of mouse and rat in; suggested development of new inbred strains of rat, *6:* 49
of multimammate mouse in, *1:* 350

Cancer Research Genetics Laboratory colony, *5:* 113
Candida albicans, *2:* 50
Canidae, *2:* 36
Cannibalism
in guinea pig, mouse, rat; prevention by diet, *3:* 62
in mouse, and transmission of toxoplasmosis, *2:* 297
in rat, and prevention, *4:* 90
Captivity
effect on rat, *1:* 7, 35, 417
effect on wild animals, *1:* 85; *2:* 36
Carbon content of tissues, measurement technique, *1:* 211
Carcass disposal, *2:* 68
see also "sanitation" *under* Housing
in radiobiologic research, *5:* 95
Cardiovascular disease research
see also Arteroisclerosis; Atherosclerosis; for diseases in animals, *see* "circulatory" *under* Diseases
use
of dog in, *2:* 215
of rat in hypertension research, *7:* 183
Care, presurgical, of animals, *7:* 172; *for care and management, see* Diets; Handling; Housing; Personnel
Caretaker, *see* Personnel
Carnivores; *see also* Animals, etc., and specific kind of animal
body, organ, gland weights, *1:* 37
care and management, *5:* 102
Carrying techniques, *7:* 33
see also Transportation
cage for mouse, rat, *5:* 54
carrier for small animals, *6:* 21
Castration
cat, of, *5:* 34
in breeding program, *4:* 84
effect
on cattle, *1:* 491; *2:* 61
on monkey, *1:* 40
on mouse, *1:* 289; *2:* 167, 272, 273
on rabbit, New Zealand, *3:* 15
on rat, *1:* 378; *2:* 232, 233, 339
Cat
blood
cholesterol, serum, *1:* 280, 474
coagulation, *1:* 12, 71, 403, 445
electrolytes, *1:* 403
Ca, Cl, phosphates, inorganic, serum, *1:* 280
erythrocytes, *1:* 12, 71, 403, 445
hematocrit, *1:* 71, 445
hemoglobin, *1:* 12, 71
hemolysis, *1:* 12
leukocytes, *1:* 12, 71, 403, 445
lipids, *1:* 403
nitrogen, nonprotein and urea, *1:* 280
picture, *1:* 74; *2:* 47
variation with age, sex, pregnancy, diet, anesthesia, species, *1:* 12
proteins, *1:* 280
age variation, *1:* 286
albumin, *1:* 403
reticulocytes, *1:* 71
sedimentation rate, *1:* 71, 403, 445
specific gravity, *1:* 12, 71
sugar, *1:* 280, 403
uric acid, *1:* 280
viscosity, *1:* 403
volume, *1:* 12, 71
blood types, *1:* 176, 467
blood vessels; cholesterol biosynthesis *in vitro*, *1:* 326
body, chemical composition of; age, sex variation, *1:* 89
body, temperature, regulation to cold; effect of restraint on, *1:* 165
body water, *1:* 95
age, sex variation, *1:* 89
body weight, gains, curves, *3:* 60
bone marrow; cellular elements in iliac crest, *1:* 74
cytology, *1:* 403
books and periodicals on
Anatomy of the Cat, *1:* 18
Atlas of Cat Anatomy, *1:* 46
Cats Magazine, *9:* 7
Complete Book of Cat Care, *1:* 162
Dissection of the Cat, *1:* 247
Index of Diagnosis for the Canine and Feline Surgeon, *2:* 54
Index of Treatment in Small Animal Practice, *2:* 69
Rabbit and Cat Diseases, *2:* 1
enzymes
cholinesterase in blood, *1:* 219
phosphatases in blood, *1:* 280
eyes
anatomy and physiology, *1:* 260
retinal circulation, *1:* 192
food consumption, *3:* 34
food preferences, *3:* 39
food requirements, *3:* 60, 68
caloric, *3:* 56, 79
standard values, *3:* 35
genetics, *1:* 162
growth curves, *3:* 60
hydropenic, physiology, *3:* 86
heat generation, *5:* 22
immune bodies, antigens in blood, *1:* 467
liver
cholesterol, *1:* 474
fat, minerals, protein, water in, age, sex variation, *1:* 89
metabolism
carbohydrate, blood sugar vs. excretion through kidney, *1:* 136
fat, mineral, protein; age, sex variation, *1:* 89
pain response, *7:* 73
physiology, *1:* 162
reproduction and sex organs, *1:* 162, 353; *5:* 117
see also "behavior patterns"; *also under* Breeding
breeding habits, *5:* 54
estrus
recognition of, *4:* 84
sexual behavior, and, *1:* 390
fetal fluid, placental type, endometrial differentiation, *1:* 267
histology and hormone output; effect of diseases on, *2:* 269
respiration
anatomy, mechanics, physiology; tables, *1:* 394
constants, *7:* 164
skull, anatomy, radiographic, *1:* 459
spleen, fat, protein, water in; age, sex variation, *1:* 89
taste response, to KCl vs. NaCl, etc., *1:* 200
vomiting, functional development of, with age, *1:* 430
water requirements, and diet relation, *3:* 86
Catching techniques
for animals, *7:* 33
floor net for laboratory rodents, rabbit, wild rat, *7:* 17
Cattle
see also Anesthesia; Animals; Breeding; Diets; Diseases; Domestic animals; Handling; Housing; Mammals; Vertebrates
adrenal glands, of calf, anatomy; histology, *1:* 489
blood
cholesterol and lipoprotein patterns in pregnancy, lactation, and in castrated, *1:* 491
coagulation, *1:* 12, 71, 445
erythrocytes, *1:* 12, 71, 445
hematocrit, *1:* 71, 445
hemoglobin, *1:* 12, 71
sulfhydryl groups, genetics of, *1:* 392
hemolysis, *1:* 12
leukocytes, *1:* 12, 71, 445, 500
picture, *2:* 47

Cattle (*continued*)
variation with age, sex, pregnancy, anesthesia, diet, species, *1:* 12
proteins, serum, *1:* 506
lipoprotein patterns, *1:* 491
reticulocytes, *1:* 71
sedimentation rate, *1:* 71, 445
specific gravity, *1:* 12, 71
volume, *1:* 12, 71
blood pressure, *1:* 368
body fat, of steer; density, *1:* 142
body temperature, rectal, skin, hair, vs. environmental temperature, *1:* 379
body water loss; vaporization, respiratory and surface, vs. environmental temperature, *1:* 379
body weight, vs. environmental temperature, *1:* 379
enzymes
cholinesterase in blood, *1:* 219; *2:* 211
glutamic oxaloacetic and pyruvic transaminases in serum and tissues, *1:* 439
succinoxidase, malic dehydrogenase in heart, kidney, liver, brain, of cow, body size variation, *1:* 143
feces, moisture loss, vs. environmental temperature, *1:* 379
food consumption, *3:* 1, 34
vs. environmental temperature, *1:* 379
food requirements of calves, caloric, *3:* 32
standard values, *3:* 35
growth, and development
effect of heat on; mechanism, *1:* 307
rates, of calves, *3:* 32
hair, growth, replacement, type, *1:* 99
immune bodies; antibodies in blood, complement, titer, *1:* 229
antigens in blood, *1:* 467
kidney, function in normal and paretic, *1:* 404
liver
biochemistry vs. body weight, *1:* 221
weight, *1:* 221
metabolism, basal, *1:* 221
vs. environmental temperature, *1:* 379
milk composition, *3:* 42
pulse rate vs. environmental temperature, *1:* 379
reproduction and sex organs, *1:* 438
fetal fluid, placental type, endometrial differentiation, *1:* 267
lactation and pregnancy, cholesterol and lipoproteins during, *1:* 491
pregnancy, leukocyte counts after parturition, *1:* 500
uterus; bactericidal activity in estrous, spayed, pseudopregnant, *2:* 61
respiratory rate vs. environmental temperature, *1:* 379
thyroid function
effect of heat; age variation, *1:* 307
vs. environmental temperature, *1:* 379
urine, moisture loss, vs. environmental temperature, *1:* 379
water consumption, *3:* 1
vs. environmental temperature, *1:* 379
Cerebrospinal fluid, *see* Spinal fluid
Cesarean section techniques, *see under* Breeding
Cetacea; body, organ, gland weights, *1:* 37
Chemical agents, use of animals in establishing limits for, *6:* 61
for toxicity in animals, *see* Diseases, "by chemical agents and drugs"
Chicken
see also Anesthesia; Animals; Birds; Breeding; Diets; Diseases; Domestic animals; Housing; Laboratory animals; Poultry; Restraint
blood
cellular elements, *2:* 47
cellular volume, *1:* 354
coagulation, *1:* 71, 403, 445
counts, numerical and differential; age variation, *1:* 17
electrolytes, *1:* 403
erythrocytes, *1:* 71, 354, 403, 445
hematocrit, *1:* 71, 445
hemoglobin, *1:* 71
electrophoretic pattern; age variation, *1:* 218
leukocytes, *1:* 71, 354, 403, 445; *2:* 225
lipids, *1:* 403
proteins, albumin, *1:* 403
effect of diet and vitamin E on, *2:* 98
γ-globulin in serum of conventional and germfree, *1:* 514
reticulocytes, *1:* 71
sedimentation rate, *1:* 71, 403, 445; *2:* 225
specific gravity, *1:* 71
of plasma, *2:* 225
sugar, *1:* 403
thrombocytes, *1:* 354
viscosity, *1:* 403
volume, *1:* 71
blood flow; coronary, renal, splanchnic fractions, *1:* 496
blood types, *1:* 467
blood vessels, cholesterol biosynthesis *in vitro*, *1:* 326
body heat generation, *5:* 22
body temperature; age variation, *1:* 17
body weight, *1:* 17
age and seasonal variation, *3:* 58
bone marrow, cytology, *1:* 403
books and films on
embryology (film), *1:* 83
Microscopic Anatomy of the Digestive System of the Chicken, *1:* 170
bursa of Fabricius, morphology of conventional and germfree, *1:* 503
digestive tract
anatomy, microscopic, *1:* 170
intestinal flora on adequate diet of conventional and germfree, *3:* 78
intestinal tract, lymphoid tissue, morphology of conventional and germfree, *1:* 503
embryology, *1:* 83
enzymes, glutamic oxaloacetic and pyruvic transaminases in serum and tissues, *1:* 439
feces, fecal flora, *1:* 246
food consumption, *3:* 1
age and seasonal variation, *3:* 58
food requirements, *3:* 8
of germfree; vitamins, *3:* 83
standard values, *3:* 35
growth, *3:* 78
heart output, *1:* 496
immune bodies
antigens in blood, *1:* 467
antihuman blood group B agglutinins, origin in germfree, *1:* 499
heterohemagglutinins, antibacterial agglutinins in sera, properdin and complement titers in conventional and germfree, *1:* 508
serum proteins, and, in conventional and germfree, *1:* 514
morphological and physiological characteristics, of germfree, *1:* 452
reproduction and sex organs, egg and sperm production; effects of light, *1:* 342
spleen, morphology, of conventional and germfree, *1:* 503
thymus, morphology, of conventional and germfree, *1:* 503
use
in experimentation, *6:* 3
in serological tests, *6:* 24
water consumption, *3:* 1
age and seasonal variation, *3:* 58
Chimpanzee, *1:* 490; *5:* 61, 123
Chinchilla, *3:* 51
Chiroptera
see also Bat
body, organ, gland weights, *1:* 37
Chloramphenicol, in treatment of disease, *2:* 153, 242
Chloroform, *see under* Anesthesia

Chlortetracycline
see also Antibiotics; Dietary additives
control, in, treatment of disease, *2:* 223, 280, 332; *3:* 17
effect
on rabbit, *2:* 92
on rat, *2:* 244, 275; *3:* 49, 69
toxicity for guinea pig, *2:* 153
Ciba Pharmaceutical Products, Inc., animal colony, *5:* 63
Climate
see also Humidity; Light; Temperature
effect on reproductive capacity of farm animals, *1:* 455
Clostridium tetani, *5:* 111
Clostridium welchii, *3:* 78
Cnemidocoptes pilae, *2:* 287
Coccidium spp., *2:* 4, 184
Cocker spaniel, *1:* 96
Collie, *2:* 96
Conferences and symposia
Design of Animal Houses, *5:* 68
Germfree Vertebrates; Present Status, *4:* 112
Growth, Replacement and Types of Hair, *1:* 99
Humane Technique in the Laboratory, *7:* 107
Infections in Laboratory Animals, *2:* 111
Infectious Diseases in Rodents, *2:* 197
Legal Environment of Medical Sciences, *6:* 63
Newer Knowledge About Dogs, *9:* 10
Nutrition of Laboratory Animals, *3:* 54
Organization and Administration of an Animal Division, *8:* 10
Production of Inbred Mice, *4:* 65
Protozoan Diseases of Man and Animals, *2:* 86
Rat Quality, *1:* 151
Constitutional strength measurement, in animals, *1:* 118
Cooling device, for dog, *7:* 72
Copulation determination, in rat, *4:* 38
Coprophagy, cage for prevention of, *5:* 5
Cortisone, *see under* Hormones
Corynebacterium kutscheri, *2:* 192
Corynebacterium murium, *2:* 132, 264
Costs and cost accounting
see also Records
of animal colonies, *5:* 102; *8:* 7, 9
of breeding
animals, *4:* 83
commercial, of mice, *8:* 1
rat colonies, littermate vs. nonlittermate, *4:* 52
of central animal care, *8:* 8
of disease- and pathogen-free
animals, *4:* 70
mice, *5:* 109, 121
rats, *4:* 49; *5:* 109
efficiency of animal division, and, *8:* 10
feed for cats, of, *4:* 98
financing and budgeting, *5:* 19
of germfree system for guinea pig, chicken, mouse, rat, *4:* 113
of guinea pig colony; accounting system, *8:* 12
of inbred mouse colony, *5:* 113
of mouse colony; accounting system, *8:* 12
of rabbit colony; accounting system, *8:* 12
of rat colony, *5:* 12
Cricetus auratus auratus, *see* Hamster
Cricetulus barabensis (Chinese hamster), *2:* 373; *4:* 81
Crowding, physiological effect of, *see under* Population dynamics
Cryptorchidism, effect on guinea pig, *1:* 272
Culture methods
see also Tissue culture
of invertebrate animals, *4:* 4
Curarization of rabbit, rectal vs. intravenous, *7:* 48
Cynomolgus monkey, *2:* 158, 165
Cyto- and histochemistry, cytology techniques, 1*:* 427; *see also* specific techniques
DA virus, *2:* 260
DDT, *see* Pesticides
Debarking technique for dog, *7:* 18
Decontamination, *see under* Housing; Radiobiologic research
Deer
see also Animals; Mammals; etc.
immune bodies; antibodies in blood, complement, titer, *1:* 229
Dehydration
effect on rat, *1:* 164
effect on renal concentrating ability of rat, *1:* 373
fluid therapy for, in cat, dog, *2:* 133
physiology of hydropenia
in cat, *3:* 86
in dog, *1:* 92; *3:* 86
Demodex canis, *2:* 320
Demodex caviae, *2:* 59
Dental clipping, effect on rat, *2:* 369
Dental research, use of germfree animals in, *6:* 60
Depilation, *see* Hair removal
Dicrocoelium lanceolatum, *2:* 188
Dietary additives
antibiotics for
cat, *3:* 60
chicken, conventional and germfree; effect of penicillin on growth of, *3:* 78
mouse; aurofac, chlortetracycline for resistance against *Salmonella*, *2:* 29
poultry; sulfaquinoxaline for control of diseases, *2:* 237
rabbit; sulfaquinoxaline for control of diseases, *2:* 237
rat
chlortetracycline,
effect of, *2:* 244, 275
placental and mammary transfer of, *3:* 49
effect on vitamin metabolism of growing, *3:* 69
penicillin, and intestinal synthesis of thiamine, *3:* 72
sulfaguanidine, *3:* 41
swine, weaned, *3:* 42
treatment of diseases, restoration of appetite, in, *3:* 17
antiseptics for rabbit; nitrofurazone for coccidiosis prevention, *4:* 93
hormones for gestating and lactating rat; effect of diethylstilbesterol on growth of young, *3:* 66
index of, *2:* 279
Dietary supplements
amino acids for infant rat, *3:* 64
bone meal for diarrhea in dog, *3:* 17
for breeding rat, *3:* 14
casein for autoclaved diet for pathogen-free animals, *4:* 87
lactose for growing rat, *3:* 48
minerals
for dog, *3:* 44
for weaned swine, *3:* 42
proteins for guinea pig, mouse, rat, and reproduction, *3:* 62
salt mixtures, commercial, for weanling inbred mouse, *3:* 27
vitamin complex for hamster, *3:* 50
vitamins
for cat, *3:* 79
for digestive disturbances in monkey, *3:* 17
for dog, *3:* 44
for guinea pig, and effect, *3:* 25
for mouse, and tolerance of, *3:* 4
for weaned swine, *3:* 42
yeast, soya oil for guinea pig, and reproduction, *3:* 62
Diets
see also under Breeding; Food; "food consumption," "food requirements," "water consumption" *under* specific kind and groups of animals
amphibia, *5:* 133
animals, including laboratory animals, *3:* 18
autoclaved and supplemented, for pathogen-free, *4:* 87
composition of, *3:* 18, 37; *5:* 57
compound, *3:* 33

Diets (*continued*)
cubed and pelleted, advantages of, *3:* 55
discussions, reviews, *1:* 101, 135, 403; *2:* 69; *3:* 54; *5:* 1, 19, 27, 28, 44, 72, 75, 76, 81, 90, 94, 102, 117; *7:* 172
diseases, and, prevention and treatment, *3:* 17
effect
on blood, *1:* 12
on production, *1:* 169; *3:* 62
evaluation of, criteria for, *3:* 56
for growth and reproduction, *3:* 63
formulas, *5:* 123
for germfree, and hand-feeding, *4:* 78
hays and straws, survey of feeding value of, *3:* 28
infertility relationship, and, *1:* 169
nutrient and energy values; tables, *3:* 35
standards, *6:* 19
and energy measure, *3:* 40
and methods of analysis, *3:* 37
birds, *1:* 135
effect on resistance to ectoparasites, *2:* 24
cat, *1:* 135, 162; *2:* 279; *3:* 60, 68; *5:* 34, 38, 76
see also Dietary additives; Dietary supplements; "animals," "domestic animals"
costs, *4:* 98
evaluation of, *3:* 56, 60
palatability tests, *3:* 39
purified, inadequacy of, *3:* 79
standards, *6:* 45
in treatment of disease, *2:* 346
chicken, *4:* 23; *5:* 76
see also Dietary additives; "birds," "poultry"
practical and synthetic for germfree, composition of; vitamin losses in sterilization, *3:* 83
resistance to infection, and, *2:* 57
standard vs. semipurified, and plasma proteins, *2:* 98
chinchilla, composition of, *3:* 51
deficient, effect of, *see under* Diseases, "nutritional"
dog, *1:* 135; *2:* 279; *4:* 14, 28, 100; *5:* 24, 76; *see also* Dietary supplements; "animals," "domestic animals"
caloric requirements, and, *3:* 30
under various conditions, *3:* 23
composition and testing, *3:* 16
daily ration, *3:* 17
in disease, *2:* 346
drinking response, and, *3:* 76
effect on spermatogenesis, and, *1:* 332
evaluation of, criteria for, *3:* 56
formulas for newborn and young, *3:* 43
ratio of meat, protein, fat, for obesity control in old age, *3:* 89
standards, *6:* 45
stock, pellets and meals, composition of, *3:* 51
supplements, and, *3:* 44
young, *3:* 75
domestic animals, *3:* 18
see also "animals," "chicken," "poultry," "sheep," "swine"
effect on reproductive capacity, and, *1:* 455
feeding standards, *3:* 40
ferret, *4:* 66
frog, *5:* 56; *see also* "amphibia"
guinea pig, *1:* 135; *3:* 13, 73, 74; *5:* 40, 76, 93, 97, 125
see also Dietary supplements; "animals"
commercial; effect on body weight, *3:* 20; *see also* "pelleted"
compressed, manufacture, and composition of, *3:* 45
dry, liquid, semisolid, evaluation for germfree, *4:* 111
evaluation of, criteria for, *3:* 56
greens
bean sprouts, *3:* 24
production of; costs, *3:* 26
vs. synthetic vitamin C additive, *3:* 25
liquid and solid for germfree, composition of, *1:* 482
Parkes' modified, composition of, *3:* 57
pelleted, commercial, and supplemented, evaluation of, *3:* 62
supplemented by greens; costs, *3:* 88
purified and stock, composition of, *3:* 31
semisynthetic for germfree, and results, *3:* 91
simplified, *3:* 5
synthetic, *3:* 74
hamster, *3:* 13; *4:* 5, 10, 81
see also Dietary supplements; "animals"
commercial vs. fresh; supplements for, and weight, *3:* 50
composition of, and, *4:* 83
effect on breeding, and, *4:* 7
simplified, inadequacy of, *3:* 11
synthetic, and purified, inadequacy of, *3:* 9
irradiated
effect on dog, *2:* 355
effect on rat, *2:* 366
monkey, *2:* 30; *5:* 61, 67, 76, 96, 104
see also Dietary supplements; "animals"
calcium, phosphorus, vitamin D excesses and effects, *2:* 174
captivity, in, *2:* 168
and disease resistance, *3:* 61
compressed, manufacture, composition of, *3:* 45
evaluation of, criteria for, *3:* 56
mouse, *1:* 135; *3:* 13, 46; *4:* 26; *5:* 76
see also Dietary additives; Dietary supplements; "animals"
amino acids and proteins in, and resistance to bacterial infection, *2:* 218
biscuit, grain mixtures, composition of, *3:* 51
commercial; effect on body weight, *3:* 20
composition of, *4:* 83
and cost, *3:* 59
compressed, manufacture, composition of, *3:* 45
concentrate, composition of, *3:* 81
cubes, composition of; comparison for breeding, *3:* 14
effect
on disease incidence, *2:* 229
on esoinophil rhythm, *1:* 150
on tumors, *2:* 16, 60
evaluation of, criteria for, *3:* 56
fox chow, oatmeal ration for inbred, and hemoglobin values, *1:* 28
in germfree and pathogen-free programs, *4:* 95; *5:* 109
pelleted, commercial, and supplemented, evaluation of, *3:* 62
resistance to infection, and, *2:* 57
semisynthetic for germfree, *3:* 91
soybean forage, estrogenic activity of, *3:* 71
spontaneous mammary cancer in C3H, and, *2:* 60
standards for inbred and random bred, *4:* 76
nutria, *5:* 118
pigeon, *1:* 311; *see also* "birds"
poultry, *5:* 49; *see also* "birds," "chicken," "domestic animals"
rabbit, *1:* 135, 254; *3:* 13; *4:* 58, 115; *5:* 76, 110
see also Dietary additives; "animals"
commercial; effect on body weight, *3:* 20
compressed, manufacture, composition of, *3:* 45
effect on reproduction, *3:* 5, 52
greens, fresh, treated with ammonia, *4:* 69
low phosphorus, and effect, *3:* 52
milk formula and sterilized, for young, *4:* 117
pelleted
age of feeding, *3:* 47
composition of, *3:* 51
with hay; costs, *3:* 88
semisynthetic for germfree; results, *3:* 91
simplified, *3:* 5
soybean forage, reproductive failures from, *3:* 71
vitamin B_{12} metabolism, and, *1:* 494
weight of weaned New Zealand, and, *3:* 15
rat, *1:* 87, 135; *3:* 13, 46; *4:* 2, 109; *5:* 12, 76
see also Dietary additives; Dietary supplements; "animals"
Bills breeding, and cannibalism prevention, *4:* 90

Diets (*continued*)
calcium and protein in maternal, and caries in offspring *2:* 120
carbohydrates in low-protein, osmotic capacity of, vs. amount consumed, *3:* 70
commercial, and effect on body weight, *3:* 20, 50
composition of, *3:* 51; *4:* 83
compressed, manufacture, composition of, *3:* 45
concentrated, composition of, *3:* 81
cubed, composition and comparison of, for breeding, *3:* 14
dry, with NaCl, urea; protein-free with Na, K, Cl variations; effect on water turnover, *1:* 493
supplemented, for breeding, *4:* 16
effect on, and, *1:* 138, 195, 483, 492
disease incidence, *3:* 62
mating performance, *4:* 22
tumor incidence, *2:* 90, 229, 240
evaluation of, *1:* 151
criteria for, *3:* 56
fats in, and ringtail incidence, *2:* 319
for inbred and random bred, *4:* 109; *5:* 76
liquid carbohydrate and tumor growth, *2:* 107
low-protein and effect of, *7:* 86
pelleted, commercial, and supplemented, evaluation of, *3:* 62
protein variations; effect on blood protein values, *1:* 510
purified, amino acid-free, *2:* 271
semipurified, evaluation of, *1:* 151
semisynthetic, for germfree; results, *3:* 91
single-food-choice; effect on weight and survival, *3:* 19
soybean oil meal, raw, for weanling, and amino acid requirement, *3:* 65
tumor incidence, and, *2:* 107, 229, 240
vitamins in; effect of environmental temperature on requirement, *3:* 10
reptiles, *5:* 133
sheep, pelleted rabbit, *3:* 51; *see also* "domestic animals"
swine, *2:* 219; *3:* 40
see also Dietary additives; Dietary supplements; "animals," "domestic animals"
evaluation of, criteria for, *3:* 56
for newborn, *3:* 42
turtle, *5:* 99, 133
Diplococcus pneumoniae, *2:* 154
Dipodomys merriami, *1:* 436
Diplidium caninum, *2:* 8
Discipline, effects on dog, *1:* 363
Disease-free animals
see also Germfree animals; Pathogen-free animals
establishment and maintenance of, *4:* 70, 82; *5:* 123
swine, *4:* 118
use in research, *4:* 105
Disease research, use of animals in, *2:* 9; *6:* 30, 55; *see also* specific type of disease
Diseases and abnormalities
See Diseases and abnormalities in animals, in domestic animals, in wild animals; Diseases and abnormalities in specific animals

---

Abstract numbers following specific types of diseases (i.e. "allergic," "bacterial," etc.) without further description usually denote books, bibliographies, discussions or reviews on this type of disease. Unless marked induced, reference is to spontaneous diseases.

Diseases and abnormalities in
amphibia, *2:* 207; *see also* Diseases and abnormalities in frog
animals, including laboratory animals
see also "domestic animals," "wild animals"
aging; pathology, *2:* 207
allergic: anaphylactic shock; mechanism, immunology, *2:* 19
bacterial
diagnosis, *2:* 47
diagnosis, resistance, immunity, *2:* 114
induced; control with UV light, *5:* 82, 101
salmonellosis; diagnosis, treatment, prevention, *2:* 235
incidence, signs, pathology, control, *2:* 121
treatment, control, and, *2:* 325
tuberculosis, induced; mortality vs. environment, *2:* 299
bone and joint, *2:* 276
books, discussions and reviews, *1:* 101, 135; *2:* 207, 353; *4:* 45; *5:* 1, 27, 76, 90, 102, 115, 117
see also under Books; Bibliographies; Conferences
chemical agents and drugs, *2:* 162, 167, 172, 347, 353
see also "books, etc."; *see also under* Anesthesia; Antibiotics; Hormones, etc.
effects on blood, *1:* 114; *2:* 12
effects on circulation, *1:* 486
toxicity of solids, liquids, gases, *2:* 347
circulatory system, *1:* 486
pernicious anemia test, *2:* 307
communicable; pathology, treatment, control, *2:* 27
congenital; defects in teeth, *2:* 337
determination of germfree status, *1:* 507
diagnosis, *2:* 83; *7:* 81
see also "books, etc."
control, and, *5:* 75, 123
histologic, *2:* 68
with radioisotopes, *2:* 307
serologic, *2:* 207
treatment, and, *2:* 83
digestive system; treatment, *2:* 325
endocrine system; treatment with hormones, *1:* 159
environmental, *5:* 108
see also Humidity; Light; Noise; Temperature
induced; pathology, *1:* 440
and longevity, *1:* 59
and mortality, *2:* 299
pathology, *2:* 207
epidemics vs. population, *2:* 214
epizoology of disease, *see under* specific disease, kind of animal
eye; treatment, *1:* 260
fungal, *2:* 291
cryptococcosis; diagnosis, *2:* 283
diagnosis, *2:* 47, 73, 199
pathology, and, *2:* 207
ringworm, and control, *2:* 246
sarcosporidiosis; diagnosis, *2:* 127
hereditary
obesity, *2:* 84
pathology, *2:* 207
incidence of, *see under* specific disease, kind of animal
infectious, *2:* 17, 111; *5:* 19
diagnosis, control, *4:* 42
isolation program for control; epidemiologic and physical aspects, *2:* 32
pathology, *2:* 207
resistance to; effect of temperature, *1:* 59
sanitation, and, *5:* 84
transmission, *2:* 32
by bats, *2:* 295
infertility, and, *1:* 169
mortality, neo- and postnatal, *4:* 56
prenatal, *4:* 55
role of disease vs. environment, *2:* 299
nutritional, *3:* 35
mineral, protein and vitamin deficiencies, *2:* 144
pathology, and, *2:* 207
parasites and; prevention, treatment, *2:* 123
parasitic
control, *5:* 27
diagnosis, and, *2:* 6, 47, 75, 112

Diseases and abnormalities (*continued*)
diagnosis
in blood, *2:* 6, 75, 143, 359; *see also* Serologic tests
in feces, *2:* 6, 75, 188, 374
in skin, *2:* 6, 75
standard operating procedure, *5:* 123
in tissues, *2:* 75
locating larvae in, *2:* 278
helminths, and control in colonies, *2:* 282
life history of ectoparasites, transmission, control, *2:* 44
nematodes; diagnosis of microfilariae, *2:* 359
pathology *2:* 207
treatment and control, *2:* 325
pathology, *2:* 72, *5:* 81
physical agents, radiation, *2:* 162, 353
effects on blood, *1:* 114
effects on circulation, *1:* 486
plants, poisonous, *2:* 162
presurgical care of, *7:* 172
prevention by decontamination with formaldehyde gas, *2:* 331
protozoan, *2:* 177
anaplasmosis; diagnosis, treatment, prevention, *2:* 86
babesiosis; diagnosis, treatment, prevention, *2:* 86
bartonellosis; diagnosis, *2:* 289
coccidiosis; treatment, prevention, *2:* 55
diagnosis, *2:* 47
incidence, pathology, treatment, *2:* 66
Encephalitozoon cuniculi; transmission, diagnosis; differentiation from toxoplasmosis, *2:* 290
toxoplasmosis; diagnosis, *2:* 138, 171, 359
diagnosis, treatment, prevention, *2:* 86
trypanosomiasis; diagnosis, *2:* 359
resistance and susceptibility, species, individual variation, *6:* 30
respiratory system; treatment, *2:* 325
spirochetal: leptospirosis; control, *2:* 343
diagnosis, serological, *2:* 270
teeth; developmental defects, *2:* 337
transmissible to man, *2:* 82, 217, 220
treatment, *2:* 69, 172; *5:* 89
antibiotics, *2:* 42
nursing of sick, *2:* 69
therapeutic drugs, index of, *2:* 279
tumors
pathology, *2:* 207
spontaneous and induced; resistance, immunity, *2:* 221
tendency to, and environmental temperature, *1:* 59
virus-induced; diagnosis, *2:* 228
viral, *2:* 114, 301
diagnosis, *2:* 47
pathology, *2:* 207
treatment and control, *2:* 325
bat
fungal: histoplasmosis; transmission to man, *2:* 220
viral: rabies; transmission by brown fat, *2:* 187
birds, *1:* 135; *2:* 2, 81
see also "chicken," "pigeon," "poultry"
bacterial; treatment, chemotherapy, *2:* 147
chemical agents; toxicity of malathion, *2:* 89
communicable, in canary; pathology, treatment, control, *2:* 27
digestive system, in caged; etiology, diagnosis, treatment, *2:* 198
fungal: mycosis, *2:* 140
of nervous system, in caged; etiology, diagnosis, treatment, *2:* 198
parasitic
arthropod; mange in parakeet; treatment, *2:* 287
arthropod; pediculosis; resistance, effect of diet on, *2:* 24
diagnosis of, *2:* 75
ectoparasitosis; control with malathion, *2:* 89
pathology, *2:* 207
physical agents: injuries, wounds, fractures; treatment, *2:* 198
protozoan: toxoplasmosis, *2:* 130
reproductive system, in caged; etiology, diagnosis, treatment, *2:* 198
respiratory system, in caged; etiology, diagnosis, treatment, *2:* 198
skin and feathers, in caged; etiology, diagnosis, treatment, *2:* 198
treatment with antibiotics, *2:* 42
tumors
in caged; etiology, diagnosis, treatment, *2:* 198
in captive wild; incidence in aged, *2:* 341
surgery, and, in caged, *2:* 321
viral
lymphomatosis, induced; diagnosis, transmission, control, *2:* 228
treatment, chemotherapy, *2:* 147
cat, *2:* 28; *4:* 45; *5:* 76, 117
see also "animals," "domestic animals"
allergic, *2:* 19
bacterial: salmonellosis; epizoology, immunology, treatment, *2:* 137
chemical agents and drugs, *2:* 162
anesthetics, *see under* Anesthesia
methemoglobin formation by acetanilide, acetophenetidine, *2:* 12
toxicity,
of griseofulvin for, *2:* 334
of malathion for, *2:* 89
of piperazine, *2:* 129
circulatory system
see also "rickettsial," "viral"
panleukopenia; diagnosis, pathology, *2:* 71
communicable; pathology, treatment, control, *2:* 27
diagnosis, and, *1:* 162; *2:* 1, 54
digestive system
see also "infectious enteritis"
gallbladder, diagnosis, radiology, *2:* 95
tumors, *2:* 146
endocrine system: tumors, *2:* 146
eye: tumors, *2:* 146
fungal, *2:* 291
favus (mouse); epizoology, transmission, *2:* 134
ringworm; diagnosis, control, transmission to man, *2:* 323
incidence, *2:* 163
treatment, *2:* 334
infectious
chronic, effect on reproductive organs, histology
treatment with antibiotics, *2:* 269
enteritis, and control, *4:* 98
prevention by sanitation and vaccination, *2:* 317
pneumonitis
control, and, *4:* 98
diagnosis, pathology, *2:* 71
prevention by sanitation and vaccination, *2:* 317
vaccination, control; differential diagnosis from other viral diseases, *2:* 348
prevention, quarantine, immunization, *2:* 124
mortality; prenatal, *4:* 55
nutritional
avitaminosis, *3:* 79
effect of malnutrition on reproductive organs; histology; treatment with antibiotics, *2:* 269
parasitic
ectoparasitism; control with malathion, *2:* 89
endoparasitism, and; diagnosis, *2:* 75
helminth
round- and tapeworms
diagnosis, incidence, treatment, pathology, *2:* 66
diagnosis, treatment, control, *2:* 236

Diseases and abnormalities (*continued*)
tapeworm, *2:* 8
treatment, piperazine, tolerated and toxic dose, *2:* 129
physical agents: injuries, wounds, fractures; treatment, *2:* 46
prevention, quarantine, *2:* 74
protozoan, *2:* 177
diagnosis, incidence, treatment, pathology, *2:* 66
toxoplasmosis, *2:* 130
diagnosis, epizoology, treatment, pathology, *2:* 285
species susceptibility, *2:* 176
reproductive system: tumors, *2:* 146
respiratory system
see also "infectious pneumonitis," "viral pneumonitis"
tumors, *2:* 146
rickettsial: hemolytic anemia by *Hemobartonella*; diagnosis, mortality, treatment, *2:* 222
skeletal system: tumors, *2:* 146
skin
see also "fungal," "parasitic ectoparasitism," "physical agents"
tumors, *2:* 146
teeth; treatment, *2:* 46
treatment, and, *1:* 162; *2:* 1, 28; *5:* 34
diet in, *2:* 346
fluid therapy, intravenous, subcutaneous, in dehydration, *2:* 133
intranasal intubation, *2:* 345
with antibiotics, *2:* 42
tumors, *2:* 88, 294
incidence, age, sex variation, *2:* 146
myxomatosis, incidence, *6:* 40
urinary system; diagnosis, radiography, *7:* 44
tumors, *2:* 146
viral
panleucopenia; diagnosis, pathology, *2:* 71
panleucopenia and pneumonitis; vaccination, control; differential diagnosis from other viral diseases, *2:* 348
pneumonitis, *see under* "infectious"
rabies; diagnosis by electrophoretic analysis of serum proteins, *2:* 76
cattle
see also "animals," "domestic animals"
allergic: anaphylactic shock; mechanism, immunology, *2:* 19
bacterial
brucellosis, and housing for immunity tests, *6:* 16
by *Escherichia coli* introduced into uterus, and bactericidal activity of uterus, *2:* 61
listerellosis, *2:* 11
salmonellosis; epizoology, immunology, treatment, *2:* 137
chemical agents and drugs, *2:* 162
organic phosphates; diagnosis, *2:* 211
fungal, *2:* 291
liver; diagnosis: function tests, *2:* 209
nervous system: postparturient paresis; effects on blood, pulse and blood pressure, adrenals; pathology, *1:* 404
parasitic; diagnosis, *2:* 75
protozoan
toxoplasmosis; epizoology, diagnosis, therapy, pathology, *2:* 285
treatment with antibiotics, *2:* 42
tumors, *2:* 88
viral: rabies; diagnosis by electrophoresis of serum proteins, *2:* 76
chicken, *4:* 23, 45; *5:* 76
see also "birds," "domestic animals," "poultry"
bacterial
listerellosis, *2:* 11
nutritional status, and, *2:* 361
pullorum, induced; signs, *1:* 17
congenital: cataracts; pathology, *2:* 358
diagnosis, *1:* 354
eye: cataracts; pathology, *2:* 358
hereditary: exudative diathesis, *2:* 98
infectious: treatment, control, *2:* 99
nutritional
deficiency disease in germfree; tissue analyses, *3:* 83
effect on infections, *2:* 361
parasitic: helminth, and nutritional status, *2:* 361
protozoan
malaria; resistance; effect of diet on, *2:* 57
nutritional status, and, *2:* 361
rickettsial, and nutritional status, *2:* 361
spirochetal, induced: leptospirosis, *6:* 24
tumors, in germfree
electronmicroscopy, *2:* 365
spontaneous, *2:* 65
transmission of induced, in conventional and germfree; effect of antibiotics on, *2:* 356
viral
eye cataracts, and lymphomatosis; pathology, *2:* 358
Newcastle; blood tests in diagnosis, *2:* 225
nutritional status, and, *2:* 361
dog, *1:* 481; *4:* 14, 45; *5:* 76, 117
see also "animals," "domestic animals"
adrenocortical insufficiency; diagnosis, *1:* 335
allergic: anaphylactic shock; mechanism, immunology, *2:* 19
bacterial
nutritional status, and, *2:* 361
pleuropneumonia in beagle; species susceptibility, *2:* 234
salmonellosis; epizoology, immunology, treatment, *2:* 137
bone
myelography, spinal, *7:* 85
radiography, spinal, *2:* 329
chemical agents and drugs, *2:* 162
anesthetics, *see under* Anesthesia
effects of drugs on, *1:* 248
methemoglobin formation by acetanilide, acetophenetidine, *2:* 12
toxicity of piperazine, *2:* 129
toxicity of piperonyl butoxide, *2:* 45
circulatory system
anemia; differential blood and bone marrow counts, *1:* 54
heart, chronic, *2:* 215
EKG, diagnosis, treatment, *2:* 141
EKG, pathology, in clinical and induced, *2:* 150
communicable; pathology, treatment, control, *2:* 27
congenital
developmental disorders of eyes, cataract, histology, *2:* 194
diagnosis, *1:* 481; *2:* 54, 330; *4:* 24; *see also* "physical examination" and diseases of organs or systems
digestive system
diagnosis, *2:* 22
diarrhea, nonspecific; diagnosis (trypsin activity), treatment, *2:* 149
gallbladder; diagnosis, radiography, *2:* 95
peritonitis, acute suppurative; differential blood and bone marrow counts, *1:* 54
treatment with antibiotics, *3:* 17
eye
blindness, *2:* 96
tumors, *2:* 294
fever, and caloric requirement, *3:* 23
fungal
favus (mouse); transmission from mice, incidence, *2:* 134
ringworm, *2:* 291
diagnosis, control; transmission to man, *2:* 323
incidence, *2:* 163
streptotrichosis; differential blood and bone marrow counts, *1:* 54
head, x-ray diagnosis, *2:* 239; *see also* "nervous system, brain"
hereditary: blindness, harelip, subluxation, *2:* 96

Diseases and abnormalities (*continued*)
infectious
diagnosis, control, *4:* 42
prevention, isolation, immunization, *2:* 124
liver
see also "viral, hepatitis"
cirrhosis, induced, and function test, *1:* 356
function tests
classification of, *2:* 145
comparison of, *2:* 316
mortality of young, *4:* 41
nervous system
brain, x-ray diagnosis, *2:* 239
diagnosis, *2:* 113
spinal fluid analysis, *1:* 207; *2:* 183
spinal myelography, *7:* 85
nutritional, effect on infections, *2:* 361
pancreas: fibrosis; differential blood and bone marrow cell counts, *1:* 54
parasitic
arthropod: mange, treatment with Aramite baths, *2:* 320
tick, and control with insecticides, *2:* 105
control, *3:* 16
diagnosis, *2:* 75
-helminth
filariasis; differential blood and bone marrow cell counts, *1:* 54
hookworm; vaccination, *2:* 312
round- and tapeworms
diagnosis, incidence, treatment, pathology, *2:* 66
diagnosis, treatment, control, *2:* 236
strongyloidiasis; treatment, *2:* 308
tapeworm, *2:* 8
Toxocara canis
clinical and induced; locating larvae in tissues, diagnosis, *2:* 308
transmission, pathology, prevention, *2:* 284
treatment with piperazine, tolerated and toxic dose, *2:* 129
nutritional status, and, *2:* 361
prevention and treatment, *2:* 26
treatment with antibiotics, *3:* 17
physical examination, *2:* 22
protozoan
by *Encephalitozoon caniculi;* transmission, diagnosis, differentiation from toxoplasmosis, *2:* 290
incidence, diagnosis, treatment, pathology, *2:* 66
nutritional status, and, *2:* 361
toxoplasmosis, *2:* 130, 177
incidence, diagnosis, pathology, therapy, *2:* 285
signs, histology, *2:* 94
species susceptibility, *2:* 176
reproductive system
obstetrics; complications, prognosis by body temperature measurement, *4:* 71
pyometra; differential blood and bone marrow cell counts, *1:* 54
respiratory system: pleuropneumonia; incidence, *2:* 234
rickettsial
hemobartonellosis in splenectomized; diagnosis, *2:* 296
hemobartonellosis, transmission, *2:* 342
nutritional deficiency, and, *2:* 361
serological diagnostic service for, *2:* 195, 292
skin: tumors; diagnosis, *2:* 351
spirochetal: leptospirosis
diagnosis, *2:* 195
immunity, vaccination, *2:* 292
surgery, *2:* 178
teeth, *1:* 22
treatment of, *1:* 481; *2:* 330; *4:* 24
antibiotics, *2:* 42
diet in, *2:* 346
fluid therapy, intravenous, subcutaneous, in dehydration, *2:* 133
tumors, *2:* 88
eye, *2:* 294
lymphoma, malignant; differential blood and bone marrow cell counts, *1:* 54
mastocytoma; diagnostic tests, *2:* 351
myxomatosis; incidence, *6:* 40
pathology, *2:* 25
skin, *2:* 351
urinary tract
kidney function test, *2:* 202; *see also* "kidney function" *under* Dog
radiography, *7:* 44, 101
viral
distemper
blood and bone marrow cell counts in nervous, *1:* 54
control, *2:* 33
diagnosis, *2:* 142, 195, 303
immunity, *2:* 230, 292
spinal fluid biochemistry and cytology in, *1:* 207
vaccination, *2:* 128
nomograph for, *2:* 195, 230, 292, 293
infectious hepatitis; control, *2:* 33
diagnosis, *2:* 142, 157, 195, 202
immunity, *2:* 292
vaccination, *2:* 128, 292
lymphocytic choriomeningitis, induced; transmission, pathology, control, *2:* 250
nutritional deficiency, and, *2:* 361
rabies
diagnosis, *2:* 76
vaccination laws in U.S., *6:* 17
domestic animals
see also "animals," "cat," "dog," etc.
aging, *2:* 185
bacterial, *2:* 185
listerellosis, *2:* 11, 185
chemical agents, *2:* 185
fungal, *2:* 185
infections, effect on reproduction, *1:* 438
legislation on, in U.S., *6:* 17
metabolic, *2:* 185
parasitic
arthropod, *2:* 185
diagnosis, host list, *2:* 112
transmission, control, *2:* 44
helminth; diagnosis, host list, *2:* 112
pathology, and, *2:* 185
physical agents
injury; diagnosis by age of bruised tissue, *2:* 367
radiation, ionizing, *2:* 185, 353
plants, poisonous, *3:* 18
protozoan, *2:* 185
reproduction, *1:* 438
rickettsial, *2:* 185
spirochetal, *2:* 185
leptospirosis; control, *2:* 343
tumors, *2:* 88, 185
viral, *2:* 185
donkey; viral: rabies; diagnosis, *2:* 76
ferret, *1:* 39, 135
communicable; pathology, treatment, control, *2:* 27
control, *4:* 66
infectious; diagnosis, control, *4:* 42
fish
pathology, *2:* 207
viral, in salmon; control, *2:* 56
fox; fungal: mouse favus; incidence, transmission, *2:* 134
frog, *4:* 45; *5:* 56
see also "amphibia"
bacterial: escherichiosis; treatment, *2:* 242

Diseases and abnormalities (*continued*)
goat
see also "animals," "domestic animals"
bacterial: salmonellosis; epizoology, immunology, treatment, *2:* 137
chemical agents and drugs, *2:* 162
toxicity of piperonyl butoxide, *2:* 45
fungal, *2:* 291
parasitic; diagnosis, *2:* 75
guinea pig, *1:* 101, 135; *4:* 45; *5:* 76, 117, 125
see also "animals," "rodents"
aging
bone marrow fatty infiltration; histology, *1:* 290
tumors, *2:* 340
allergic: anaphylactic shock; mechanism, immunology, *2:* 19
bacterial, induced
brucellosis; airborne transmission, *2:* 117
incidence, mortality, pathology, control, *2:* 43
listerellosis, *2:* 11
nutritional deficiency, and, *2:* 361
salmonellosis, by contaminated feed, *2:* 40
transmission through conjunctiva, *2:* 180
tuberculosis, induced vs. spontaneous disease; mortality, role of environment vs. disease in, *2:* 299
bone and joint, *2:* 276
chemical agents and drugs, *2:* 162
anesthetics, *see under* Anesthesia
antibiotics, *2:* 119, 153
in hair, *2:* 322
dusts, and, induced; lung pathology, *2:* 324
pyrogens, sensitivity to, *6:* 34
communicable; pathology, treatment, control, *2:* 27
control in colonies, *5:* 97
endocrine, see "tumors"
fungal, *2:* 291
and antibiotic in hair after treatment, *2:* 322
induced; immunization, *2:* 335
moniliasis, induced; susceptibility, *2:* 50
ringworm, induced; treatment with antibiotics, *2:* 227
sarcosporidiosis; diagnosis, *2:* 127
hereditary
spermatogenic hypoplasia; incidence, pathology, *2:* 241
infectious, in breeding units; diagnosis, control, *4:* 42
liver, edema in young; pathology, control, *2:* 186
morbidity, mortality; effect of diet, *3:* 62
mortality in breeding colony, *4:* 12, 39, 55
muscle, inflammation, *2:* 267
nervous system, by magnesium deficiency; effect of Ca and P on, *2:* 258
nutritional, *3:* 57, 74
choline deficiency; mortality, pathology, *2:* 191
effect on infections, *2:* 361
incidence, mortality, pathology, *3:* 62
mineral (Mg) deficiency, *2:* 258
parasitic,
arthropod
lice; incidence, mortality, pathology, control, *2:* 43
mites, *2:* 59
diagnosis, *2:* 75
helminth, roundworms; diagnosis, incidence, treatment, pathology, *2:* 66
diagnosis, treatment, control, *2:* 236
incidence in conventional and germfree, *2:* 349
oxyuriasis; incidence, treatment, *2:* 31
nutritional deficiency, and, *2:* 361
physical agents
heat, survival in, *1:* 361
injury, effect on bleeding time and capillary resistance, *2:* 15
injury by foreign body in food; lung pathology, *2:* 109
injury, treatment of viral infection, *2:* 262
protozoan
amebiasis, induced, in conventional and germfree, *2:* 352
coccidiosis; incidence, treatment, *2:* 31
diagnosis, incidence, treatment, pathology, *2:* 66
and treatment, *2:* 177
Encephalitozoon cuniculi; transmission, diagnosis, differentiation from toxoplasmosis, *2:* 290
incidence, mortality, pathology, control, *2:* 43
by *Klossiella cobayae*, induced; kidney pathology, *2:* 210
nutritional deficiency, and, *2:* 361
toxoplasmosis; species susceptibility, *2:* 176
reproductive system: spermatogenic hypoplasia, *2:* 241
tumors by hormone imbalance; histopathology, *2:* 340
respiratory system
lung edema, *1:* 189
pathology, induced, by avirulent tubercle bacilli, chemical agents, *2:* 324
rickettsial; and nutritional deficiency, *2:* 361
salivary gland; histopathology, *2:* 208
skin
see also "fungal," "parasitic"
by mineral (Mg) deficiency; effect of Ca and P on, *2:* 258
tumors; incidence in aged, by hormone imbalance; pathology, *2:* 340
unknown origin; incidence, mortality, pathology, control, *2:* 43
liver edema in young; pathology, *2:* 186
myositis; pathology, *2:* 267
viral; incidence, mortality, pathology, control, *2:* 43
lymphocytic choriomeningitis; transmission, pathology, control, *2:* 250
mouse pox, ectromelia; resistance to, *2:* 265
nutritional deficiency, and, *2:* 361
rabies, induced; prevention by treatment of wounds, *2:* 262
salivary gland; transmission, histopathology, *2:* 208
hamster
see also "animals," "rodents"
aging; bone necrosis, pathology; genetic, sex factors, *2:* 277
bacterial
salmonellosis; incidence, transmission, pathology, *2:* 108
bone and joint, *2:* 276
bone necrosis; pathology, *2:* 277
chemical agents: antibiotics, *2:* 119
communicable; pathology, treatment, control, *2:* 27
control, and, *5:* 117
digestive tract; incidence, *2:* 245
epizoology, *2:* 245
eye; incidence, *2:* 245
fungal, *2:* 291
hereditary metabolic: diabetes mellitus in inbred Chinese; pathology; strain variation, *2:* 373
mortality in hibernation, *1:* 238
mouth: teeth and gums; system for recording, *1:* 156
nutritional: avitaminosis; mortality, pathology, *3:* 11
parasitic
arthropod: mites; control with insecticides, *2:* 268
helminth: diagnosis, treatment, control, *2:* 236
by *Nippostrongylus muris*; resistance to, *2:* 238
physical agents
injuries; incidence, *2:* 245
injuries by fish bone in food; lung pathology, *2:* 109
protozoan; diagnosis, treatment, *2:* 177
reproductive system; incidence, *2:* 245
respiratory system; incidence, *2:* 245
skin; incidence, *2:* 245
teeth, *see* "mouth"
tumors
incidence, *2:* 245
myxosarcoma, transplanted, in inbred, *2:* 62
horse
see also "animals," "domestic animals"
allergic: anaphylactic shock; mechanism, immunology, *2:* 19

Diseases and abnormalities (*continued*)
bacterial: listerellosis, *2:* 11
salmonellosis; incidence, immunology, treatment, *2:* 137
chemical agents and drugs, *2:* 162
fungal, *2:* 291
liver; diagnosis, *2:* 344
parasitic; diagnosis, *2:* 75
treatment with antibiotics, *2:* 42
tumors, *2:* 88
viral: rabies, diagnosis, *2:* 76
monkey, *1:* 135; *2:* 360; *4:* 45; *5:* 61, 76, 117
see also "animals"
allergic, *2:* 19
bacterial
dysentery, pneumonia, *2:* 97
epizoology, pathology, treatment, *2:* 67
nutritional status, and, *2:* 361
tuberculosis, *2:* 97; *5:* 104
control, *2:* 70
diagnosis, *2:* 7, 30; *5:* 123
and treatment, *2:* 35
bone and joint: rickets, osteomalacia; treatment, *2:* 168
chemical agents
methemoglobin formation by acetanilide, acetophenetidine, *2:* 12
toxicity of piperonyl butoxide for, *2:* 45
communicable; pathology, treatment, control, *2:* 27
control by isolation, *2:* 30, 32
digestive system
by faulty diet; treatment, *2:* 35
treatment with antibiotics, *3:* 17
fungal, *2:* 291
diagnosis, treatment, control, *5:* 104
incidence, pathology, in rhesus and cynomolgus, *2:* 165
in new arrivals, isolation and treatment, *2:* 30
nutritional
control, and, *2:* 35; *3:* 61
effect on infections, *2:* 361
hypervitaminosis D; signs, pathology, *2:* 174
treatment, *2:* 35
vitamin D deficiency; treatment with UV, *2:* 168
parasitic
arthropod: by *Pneumonyssus foxi*; transmission, *2:* 158
control, *2:* 30
epizoology, pathology, treatment, *2:* 67
helminth; diagnosis, treatment, control, *2:* 236; *5:* 104
oesophagostomiasis; incidence, treatment, *2:* 31
roundworms; diagnosis, incidence, treatment, pathology, *2:* 66
strongyloidiasis; incidence, treatment, *2:* 31
worms; treatment, *2:* 35
physical agents: radiation, tumors, *2:* 243
protozoan
balantidiasis; incidence, treatment, *2:* 31
diagnosis, incidence, treatment, pathology, *2:* 66
diagnosis, treatment, control, *2:* 35; *5:* 104
malaria, *2:* 14
nutritional status, and, *2:* 361
respiratory system
control, *2:* 70
Pneumonyssus foxi; transmission, *2:* 158
rickettsial, and nutritional status, *2:* 361
skin; tuberculosis by contamination in tattooing, *2:* 193
treatment with antibiotics, *2:* 42
tumors, spontaneous and radiation-induced
incidence, distribution, *2:* 243
viral, *2:* 97
epizoology, pathology, treatment, *2:* 67
lymphocytic choriomeningitis; transmission, pathology, control, *2:* 250
nutritional status, and, *2:* 361
mouse, *1:* 44, 101, 135; *4:* 45; *5:* 76
see also "animals," "rodents"
aging
bone necrosis; incidence, pathology; genetic, sex factors, *2:* 277
degeneration, and; pathology, *1:* 174
degenerative joint, in inbred; sex variation, *2:* 272
osteoarthritis in inbred; sex variation, *2:* 273
bacterial
Corynebacterium murium, spontaneous, induced; pathology, *2:* 132
Diplococcus pneumoniae, spontaneous, induced; vaccination, treatment with antibiotics, *2:* 154
effect of diet on resistance to, *2:* 218, 361
enterococcal hepatitis, spontaneous, induced; susceptibility, effect of cortisone on, *2:* 39
Escherichia coli, induced; lung pathology, *2:* 328
Klebsiella pneumoniae, spontaneous, induced, *2:* 156
Pasteurella hemolytica: vaccination, antibody response, *2:* 363
pleuropneumonia; species susceptibility, *2:* 234
PPLO; epizoology; signs, diagnosis, *2:* 254
pneumococcosis; effect of temperature on resistance to, *1:* 47
respiratory, chronic; transmission, control, *2:* 181
spontaneous and induced; treatment with antibiotics, *2:* 154
salmonellosis
diagnosis, *2:* 274
diagnosis, immunization, treatment; effect of environment, diet, genetic selection on, *2:* 29
and treatment, *2:* 23
effect of diet on resistance to, *2:* 57
epizoology; prevention, *5:* 121
in inbred; vaccination, *2:* 34
induced; pathology, *2:* 108
Salmonella spp. feed contamination, *2:* 40
spinning disease, induced by Pseudomonas, Mycobacteria, and Nocardia, *2:* 100
Tyzzer's disease by *B. piliformis*; pathology, control, age variation, *2:* 266
bone and joint, *2:* 276
incidence, age, sex variation in inbred, *2:* 272
necrosis; pathology, genetic, sex variation, *2:* 277
osteoarthritis in inbred; incidence, age, sex variation, *2:* 273
chemical agents and drugs, *2:* 162
anesthetics, *see under* Anesthesia
antibiotics, *2:* 119
drug toxicity; effect of temperature on, *2:* 10
circulatory
eosinopenia in and after pregnancy, *1:* 149
myocarditis, pathology, *2:* 261
pulmonary arteritis, pathology, *2:* 261
communicable
diagnosis, control, *4:* 42
pathology, treatment, control, *2:* 27
resistance to, *1:* 110
congenital, *2:* 160
cleft palate in inbred, incidence in offspring after cortisone injection to mother, *4:* 17
monstrosities, *1:* 415
polydactylism, syndactylism, hydrocephalus, tail, *2:* 37
control, and, *5:* 117
and prevention in breeding units, *4:* 26
diagnosis, prevention in breeding stock; standards for inbred and random bred, *4:* 76
digestive system
diarrhea, epizootic, *see under* "viral"
prolapsed rectum; surgical replacement, *2:* 310
ear, *2:* 181
see also under "parasitic"
spinning disease, *2:* 100
endocrine: diabetes; *see under* "metabolic"
epizootics, control of, *2:* 122
eye: blindness;

Diseases and abnormalities (*continued*)
effect on estrus, *4:* 116
congenital and induced; body temperature rhythms in, *1:* 182
fungal, *2:* 291
favus, epizoology, *2:* 134
Microsporum epidermidis, induced; mortality, *4:* 95
ringworm, transmission to man, *2:* 217
hereditary, *1:* 110
leukopenia in inbred and hybrids, *2:* 139
muscular dystrophy; signs, treatment, *2:* 200
myxedema, secondary, *1:* 509
obese-hyperglycemic syndrome, and sensitivity to cold, *1:* 173
incidence in breeding colony, pathology, *2:* 264
effect of diet on, *3:* 62
liver
Tyzzer's disease; age variation, pathology, control, *2:* 266
lymph nodes: *Klebsiella* infection, spontaneous, induced, *2:* 156
mammary gland: tumors; cytology, morphology, histogenesis, genetics; effect of diet on, *2:* 16
metabolic
diabetes, alloxan-induced; glucose tolerance tests; strain variation, *1:* 191
hyperglycemic syndrome, genetic, in obese inbred, *1:* 341; *2:* 84
mortality, in breeding colony, *4:* 39
causes of, in inbred and germfree, *3:* 85; *4:* 95
effect of diet on, *3:* 62
neonatal, *4:* 75
pre- and postnatal, in breeding colony, *1:* 330; *4:* 55
nervous system: encephalomyelitis; pathology, *2:* 260
nutritional, effect of deficiency, excess, on incidence, mortality, pathology in infections, infestations, *2:* 361; *3:* 62
obesity, induced and genetic; mechanisms and reproduction, *2:* 84
parasitic
arthropod
ear mange; treatment, *2:* 87
epizoology, morphology, pathology, prevention, *2:* 79
mange, follicular; treatment, *2:* 318
mites; control; malathion compared with lindane, *2:* 368
Myocoptes musculinus, *Myobia musculi*; morphology, control, *2:* 38, 48
myocoptic; diagnosis, treatment, *2:* 64
helminth
diagnosis, *2:* 75
diagnosis, treatment, control, *2:* 236
nutritional deficiency, and, *2:* 361
oxyuriasis; elimination with piperazine, *2:* 327
incidence, treatment, *2:* 31, 85, 166, 190
round-, tapeworms, etc.
diagnosis, incidence, treatment, pathology, *2:* 66
teniasis; incidence, treatment, *2:* 31
trichinosis, induced; resistance vs. population density, *2:* 214
worms; treatment, *2:* 129
physical agents
cold, heat, mortality in, *1:* 330
injuries from fighting; effect on adrenals, *2:* 305
reaction to injury; pathology, *1:* 174
protozoan, *2:* 177
coccidiosis; incidence, treatment, *2:* 31
diagnosis, incidence, treatment, pathology, *2:* 66
Encephalitozoon cuniculi; signs, incidence, transmission, *2:* 249
transmission, diagnosis; differentiation from toxoplasmosis, *2:* 290
and nutritional deficiency, *2:* 361
toxoplasmosis, induced; transmission to young, congenital defects, *2:* 160
immunology, treatment, *2:* 159
transmission, *2:* 297
treatment, *2:* 77, 78, 203
drug evaluation, *2:* 152, 263
respiratory system
mortality in cesarean-born and hand-reared, *3:* 85
see also under "viral"
PPLO and viral, spontaneous, induced; transmission, control, *2:* 181
rickettsial
Eperythrozoon, induced, *2:* 164
nutritional deficiency, and, *2:* 361
skin, nonparasitic, *2:* 79; *see also* "fungal," "parasitic, arthropod"
spirochetal
Leptospira ballum; transmission, eradication with antibiotics, *2:* 280
Leptospira ballum, induced; antibody in sera, *2:* 371
treatment with antibiotics, *2:* 42
tumors, *1:* 44; *2:* 65
genetics of, *1:* 110
incidence, effect of cage, plastic vs. metal, on, *5:* 80
effect of diet on, *2:* 60
on thyroid function; histology, *1:* 377
in inbred, vs. age; effect of hormones on, *4:* 101
mammary
cytology, morphology, histogenesis, genetics; effect of diet on, *2:* 16
incidence in inbred and hybrids; mean tumor age; age and strain variation, *2:* 357
mortality due to, in inbred, germfree, *4:* 95
pathology, *1:* 174
recording of spontaneous, *2:* 65; *4:* 59
resistance to, *6:* 49
unknown origin: myocarditis, pulmonary arteritis; pathology, *2:* 261
viral
diarrhea, epizootic
(suspected), *2:* 20
in suckling, *2:* 21, 224
mortality, pathology, *2:* 259
strain variation, and, *2:* 21
ectromelia
diagnosis, epizoology, vaccination, control, *2:* 118, 265, 300
encephalomyelitis; pathology, *2:* 260
hepatitis, induced; ascites, virulence, *2:* 91
latent; activation by *Eperythrozoon coccoides* inoculation, *2:* 80
lymphocytic choriomeningitis, spontaneous, induced; transmission, pathology, control, *2:* 250
pneumonitis; resistance to, effect of diet on, *2:* 57
rabies, induced
diagnosis, *2:* 76
transmission by bats, *2:* 295
respiratory, chronic
enzootic bronchiectasis; transmission, control, *2:* 181
Theiler's encephalomyelitis; incidence, natural immunity, histopathology, *2:* 251
nutria, *5:* 118
opossum; fungal, *2:* 291
pigeon, *1:* 311
see also "birds"
allergic, *2:* 19
circulatory (of aging; hereditary)
atherosclerosis; breed variation, *2:* 306; *6:* 53
communicable; pathology, treatment, control, *2:* 27
poultry, *2:* 83, 298
see also "birds," "chicken," "domestic animals"
bacterial
salmonellosis; epizoology, signs, immunology, treatment, *2:* 137
tuberculosis; test, wattle, *2:* 226

Diseases and abnormalities (*continued*)
chemical agents: poisonings, *2:* 298
fungal, *2:* 291
laboratory conditions, under, *5:* 49
protozoan
toxoplasmosis; epizoology, diagnosis, pathology, therapy, *2:* 285
surgery, *2:* 298
tumors, *2:* 298
rabbit, *1:* 101, 135, 254, 263 (wild); *2:* 1, 5, 9; *4:* 45, 58; *5:* 76, 117
see also "animals," "wild animals"
allergic, *2:* 19
anaphylactic shock; pathology, *2:* 106
bacterial, *2:* 5, 135
brucellosis; incidence, pathology, serology, *2:* 182
control, treatment, *2:* 116
escherichiosis, spontaneous, induced; treatment; susceptible species, *2:* 242
listerellosis, *2:* 11
nutritional status, and, *2:* 361
pseudotularemia; signs, pathology, mortality, age, *2:* 161
respiratory; diagnosis, eradication, pathology, *2:* 41
by *Pasteurella, Alcaligenes, Micrococcus,* induced; epizoology, treatment, *2:* 326
salmonellosis
diagnosis, histopathology, *2:* 110
induced; pathology, *2:* 108
bone and joint
pathology, *2:* 276
splayleg, pathology, *2:* 169
brain, *see* "congenital"
chemical agents and drugs, *2:* 162
sensitivity to pyrogens, *6:* 34
communicable; pathology, treatment, control, *2:* 27
congenital: hydrocephalus by hypovitaminosis in mother, *2:* 179
diagnosis of, by electrophoresis of serum proteins, *1:* 323
digestive, by unknown agent, *2:* 135
eye, *2:* 102
fungal, *2:* 135, 291
histoplasmosis, induced; course, *2:* 315
moniliasis, induced; species susceptibility, *2:* 50
ringworm, *2:* 116
Saccharomycopsis guttulata; signs, diagnosis, treatment, *2:* 103
sarcosporidiosis; diagnosis, *2:* 127
hereditary
eyes, *2:* 102
splayleg; pathology, *2:* 169
incidence in breeding stock, *4:* 18
mortality
in breeding colony, *4:* 18, 55
in Gt. Britain, California, *2:* 116
nutritional, by deficient, excessive nutrients
effect on infections, *2:* 361
estrogens in soya bean foliage, *3:* 71
germfree young fed milk formula, sterilized diet; pathology, *4:* 117
hypovitaminosis, maternal, effect on offspring, *2:* 179
vitamin deficiency
A; effect on eyes, *2:* 102
D and; treatment, control, *2:* 116
factor in *Saccharomycopsis guttulata* infection, *2:* 103
B; effects, mortality, *3:* 53
E; effect on heart of New Zealand giant, *1:* 97
parasitic
arthropod: mites (mange), treatment, control, *2:* 116
arthropod and helminth; diagnosis, control, *2:* 75, 135, 236
diagnosis, transmission, control, pathology, *2:* 4
nutritional status, and, *2:* 361
physical agents
cold and heat, mortality in, *1:* 14
lung injury by fish bone in food; pathology, *2:* 109
protozoan
coccidiosis, *2:* 177
breeding, in; prevention, *4:* 69, 93
diagnosis
by electrophoresis of serum proteins, *1:* 323, *2:* 313
incidence, treatment; pathology, *2:* 66
treatment, *2:* 204
effect of continuous feeding of sulfaquinoxaline on mortality of infants, adults, *2:* 237
induced; treatment, *2:* 136, 184; *3:* 17
treatment, control, *2:* 116
Encephalitozoon cuniculi; transmission, *2:* 249
diagnosis, transmission; differentiation from toxoplasmosis, *2:* 290
nutritional status, and, *2:* 361
toxoplasmosis, *2:* 130
induced; treatment, *2:* 131
species susceptibility, *2:* 176
reproductive system, *2:* 135
by *Escherichia coli*, induced; uterine resistance to, *2:* 61
respiratory system, *2:* 135
see also under "bacterial"
lung pathology by fish bone in food, *2:* 109
pneumonia, pasteurellosis; effect of continuous feeding of sulfaquinoxaline on mortality, incidence, *2:* 237
snuffles; treatment with antibiotics, *3:* 17
rickettsial, and nutritional status, *2:* 361
skin: follicular keratosis; signs, histology, treatment, *2:* 52
see also "fungal," "parasitic, arthropod"
spleen: salmonellosis, *2:* 110
treatment with antibiotics, *2:* 42
urinary system, *2:* 135
viral
diagnosis, control, *2:* 135
ectromelia (mouse pox); resistance to, *2:* 265
myxomatosis; treatment, control, *2:* 116
transmission by arthropods; mortality, control, *2:* 53
nutritional status, and, *2:* 361
rabies; diagnosis by serum protein electrophoresis, *2:* 76
rat, *1:* 45, 101, 135; *4:* 2, 45; *5:* 12, 76, 117
aging, *2:* 370
bone necrosis; pathology; genetic, sex factors, *2:* 277
effect on blood, *1:* 359; *2:* 233
food intake, and, *2:* 18
and water intake, elimination, *3:* 67
heart; pathology, *1:* 277, 358
kidney; pathology, *1:* 277; *2:* 126
and protein excretion, *1:* 357
liver, fatty, *1:* 277; *2:* 232
allergic, *2:* 19
bacterial, *4:* 72
by *Brucella bronchiseptica*; vaccination, *2:* 288
by *Corynebacterium kutscheri*; susceptibility to, in pantothenate deficiency; body size variation, *2:* 192
keratoconjunctivitis; transmission, treatment, *2:* 223
otitis media; incidence, diagnosis, *4:* 96
panophthalmitis; incidence vs. age; treatment, *2:* 332
pleuropneumonia; treatment, prophylaxis, *2:* 206
PPLO polyarthritis, *2:* 170
pseudotularemia, *2:* 161
respiratory by PPLO; transmission, diagnosis, control, *2:* 181, 254
bone and joint, *2:* 254, 276
necrosis; genetic, sex factors; pathology, *2:* 277
polyarthritis, *2:* 170
chemical agents and drugs, *2:* 162
drugs; effect on growth, *3:* 41
dusts, induced i.t., and; lung pathology, *2:* 324
hormone injections, pathology; sex variation, *2:* 286
methemoglobin formation, and, *2:* 12
thiourea toxicity; resistance to, *7:* 121

Diseases and abnormalities (*continued*)
toxicity, i.p., effects of temperature on, *2:* 336
of piperonyl butoxide, *2:* 45
circulatory: anemia, *2:* 3
hypertension
induced, *7:* 183
sex variation; repeated pregnancy and incidence, *2:* 370
communicable; pathology, treatment, control, *2:* 27
congenital
hydrocephalus by maternal hypovitaminosis; histopathology, *2:* 255
malformations by maternal avitaminosis E; treatment with hormones, *2:* 304
maternal toxoplasmosis, *2:* 160
diagnosis and prevention, in pathogen-free, *4:* 68
standards for random and inbred, *4:* 109
digestive system
epizootic diarrhea in suckling, *2:* 224
stomach ulcers, incidence, *2:* 370
ear
infection; pathology, control by quarantine, *4:* 19
otitis media; incidence, diagnosis, control, *2:* 101; *4:* 96
PPLO
diagnosis, transmission, *2:* 254
epizoology, pathology, *2:* 181
eye
keratoconjunctivitis; treatment, *2:* 223
purulent panophthalmitis; incidence vs. age; treatment, *2:* 332
fungal, *2:* 291
moniliasis, induced; susceptibility, *2:* 50
Rhizopus oryzae; treatment, *7:* 115
ringworm; epizoology; effect of breeding, care, handling practices on, *2:* 309
and transmission to man, *2:* 217
incidence, age variation, *2:* 366
effect of diet on, *3:* 62
effect of repeated pregnancy on; age variation, *2:* 370
mammary gland, *see* "tumors"
metabolic, stress, by repeated pregnancy, rapid aging; pathology, sex variation, *2:* 286
mortality, in colony, *2:* 51
effect
of diet on, *3:* 62
of housing on conventional and germfree, *4:* 95
prenatal, *4:* 55
wild gray Norway, in, *1:* 35
nervous system
by deficiency or excess in nutrients, *see* "nutritional"
demyelinating disease by JMH virus; pathology, *2:* 260
nutritional
amino acid deficiency
induced; pathology, *1:* 492; *2:* 271
in infant; signs, *3:* 64
anemia in black, black hooded, gray coated; color change; restoration with Cu, Fe, *2:* 3
avitaminosis; effect on louse infestation, *2:* 24
deficiency and excess of nutrients; effect on infections, *2:* 361
diarrhea from lactose diet; effect of antibiotics on, *2:* 244
hypervitaminosis; signs, *2:* 354
incidence; mortality, pathology, *3:* 62
mineral deficiency
Mg; signs; effect of Ca, P, on, *2:* 258
Mn; and righting reflex in offspring, *1:* 462
and effect on serum phosphatase, *1:* 463
Na, K; signs, pathology; effect of NaCl on, *2:* 148
Zn; signs, *2:* 252
protein deficiency
effects, pathology, *2:* 104
liver hypertrophy in lactating, *2:* 104
signs, *2:* 201
vitamin deficiency
B_{12}
diagnosis, *1:* 406
in mother from weaning, and hydrocephalus in offspring; histopathology, *2:* 255
E, in mother; and malformations in offspring, *2:* 304
K; effect of temperature on, *2:* 13
pantothenate; effect on bacterial infection, *2:* 192
riboflavin, thiamine, in growing; effect of antibiotics on food consumption, *3:* 69
thiamine, and nerve degeneration, *2:* 115
parasitic
arthropod
effect of diet on resistance to louse infestation, *2:* 24
helminth, and
diagnosis, life history, *2:* 75
diagnosis, treatment, control, *2:* 236
control, *4:* 72
helminth
Nippostrongylus muris; resistance, *2:* 238
nutritional status, and, *2:* 361
oxyuriasis; incidence, treatment, *2:* 31, 166
round-, tapeworms, etc.; diagnosis, incidence, treatment, pathology, *2:* 66
teniasis; incidence, treatment, *2:* 31
Trichinella spiralis; transmission, diagnosis, *2:* 189, 374
mortality and control, *4:* 49
pathology, *1:* 2
physical agents
environmental, humidity, and ringtail in infant, *2:* 216, 281, 319; *4:* 77
environmental, temperature
cold and heat, and survival in traumatic shock, *2:* 151
heat, and longevity, *1:* 361; *2:* 302
heat, and mortality, *1:* 195, 449
injury inducing shock; effect of temperature on survival, *2:* 151
lung injury by bone particles in food; pathology, *2:* 109
radiation and heat; effect on longevity, *2:* 302
protozoan, *2:* 177
coccidiosis; incidence, treatment, *2:* 31
diagnosis, incidence, treatment, pathology, *2:* 66
Encephalitozoon cuniculi; transmission, diagnosis, differentiation from toxoplasmosis, *2:* 290
nutritional status, and, *2:* 361
toxoplasmosis, *2:* 130
induced
effect on serum proteins, *1:* 512
in multimammate; species susceptibility, *2:* 176
transmission to young, fetal defects, *2:* 160
trypanosoma infection, induced; blood pyruvate as measure of parasitemia, *2:* 143
reproductive: abortion, fetal resorption, *1:* 209, 312
respiratory, natural history of, *1:* 151
pathology, induced, by avirulent tubercle bacilli, chemical agents, *2:* 324
pleuropneumonia (PPLO); control by quarantine, *4:* 19
pneumonia
incidence, age, *2:* 366
(infectious); mortality, control, *4:* 49
(infectious); prevention in breeding colony, *4:* 29
transmission, pathology, control, *2:* 181
rickettsial
bartonellosis
incidence, transmission by arthropods, *2:* 231
resistance, splenic protection, *2:* 311
control, *4:* 72
nutritional status, and, *2:* 361
skin
by mineral (Mg) deficiency; effect of Ca, P on, *2:* 258
ringtail in infant, *2:* 216, 281, 319; *4:* 77
teeth; caries susceptibility and maternal nutrition, *2:* 120

XUM

Diseases and abnormalities (*continued*)
tumors, *2:* 65
adrenal cortex, in inbred; incidence, *1:* 376
carcinomas, sarcomas (film), *1:* 83
incidence, in aging; pathology, sex variation, *2:* 370
pathology vs. food consumption, body weight; mortality, *2:* 51
site, and
effect of gonadectomy, x-ray, hormones on, *2:* 339
pathology, *2:* 212
strain variation; effect of diet, environment on, *2:* 229
mammary, *2:* 350
incidence vs. age, sex, diet; mortality, *2:* 90
thyroid; incidence vs. age; effect of diet on, *2:* 240
viral
ectromelia (mouse pox); resistance to, *2:* 265
enzootic bronchiectasis; transmission, control, *2:* 181
JHM virus, demyelinating disease; pathology, *2:* 260
lymphocytic choriomeningitis, spontaneous, induced; transmission, pathology, control, *2:* 250
nutritional status, and, *2:* 361
rabies, induced; diagnosis by serum protein electrophoresis, *2:* 76
reptiles
see also "turtle"
bacterial
salmonellosis; epizoology, immunology, treatment, *2:* 137
pathology, *2:* 207
rodents
see also "animals," "guinea pig," "hamster," "mouse," "rat"
bacterial
salmonellosis; epizoology, immunology, treatment, *2:* 137
fungal
ringworm, in wild; incidence, effect of environment on, *2:* 248
infectious, *2:* 197
tumors, spontaneous and induced, *2:* 221
sheep
see also "animals," "domestic animals"
bacterial
listerellosis, *2:* 11
salmonellosis; epizoology, immunology, treatment, *2:* 137
chemical agents and drugs, *2:* 162
fungal, *2:* 291
sarcosporidiosis; diagnosis, *2:* 199
parasitic, arthropod and helminth; diagnosis, *2:* 75
protozoan
toxoplasmosis; epizoology, diagnosis, pathology, therapy, *2:* 285
tumors, *2:* 88
viral: rabies; diagnosis by serum protein electrophoresis, *2:* 76
swine, *2:* 219
see also "animals," "domestic animals"
bacterial
listerellosis, *2:* 11
rheumatoid arthritis, spontaneous and induced, *2:* 253
salmonellosis; epizoology, immunology, treatment, *2:* 137
chemical agents and drugs, *2:* 162, 219
fungal, *2:* 291
mortality, prenatal, *4:* 55
nutritional, in infant; mortality, *3:* 36
parasitic
arthropod and helminth; diagnosis, *2:* 75
helminth: ascariasis; control by soil treatment, *2:* 362
Trichinella spiralis; transmission, fecal examination, *2:* 374
surgical techniques for, *2:* 219
treatment with antibiotics, *2:* 42
tumors, *2:* 88
viral: lymphocytic choriomeningitis, spontaneous, induced; transmission, pathology, control, *2:* 250
turtle, *5:* 99
see also "reptiles"
bacterial
escherichiasis, *2:* 173
treatment, *2:* 242
nutritional: eye infection, shell softness by mineral deficiency; control, *2:* 364
wild animals, *2:* 81
captive, *2:* 2
due to inactivity; shock, histology, *2:* 36
fungal: ringworm
effect of environment on, *2:* 248
epizoology, *2:* 247
spirochetal: leptospirosis; control, *2:* 343
treatment, *2:* 372
tumors; incidence in aged, *2:* 341
viral: myxomatosis in rabbit, *1:* 263
Disinfection, in small animal practice, *2:* 69
see also under Housing
principles of, in animal care, *5:* 84
Disinfestation, *see* Parasites, control; "pest control" *under* Housing; *see also under* Diseases, "parasitic"
Dissection techniques, *1:* 247
see also Necropsy techniques
dog, *1:* 113
rabbit, *1:* 81, 266
rat, *1:* 266
Dithiazinine, in treatment of strongyloidiasis in dog; effectiveness and safety, *2:* 308
Dog
see also Anesthesia; Animals; Breeding; Diets; Diseases; Domestic animals; Handling; Housing; Laboratory animals; Mammals; Restraint; Vertebrates
adrenal glands
anatomy, comparative; histology, *1:* 489
blood flow, *1:* 215
function, *1:* 335
steroids in blood, function, *1:* 141
anatomy, *1:* 135, 481; *2:* 178
and dissection, *1:* 113
topographical, *1:* 428
behavior patterns, *4:* 24; *6:* 28
abnormal, *1:* 319
adjustive and sexual, breed and environmental variation, *1:* 144
biting, *8:* 15
effects of discipline on, *1:* 363
exploratory activity; effect of restriction on, age variation, *1:* 196
vs. population dynamics, *1:* 107
whirling in isolated, *1:* 264
bile, cholesterol, *1:* 474
blood
cell counts of peripheral, *1:* 51
cellular elements, *1:* 153; *2:* 47
cholesterol, plasma, *1:* 275
see also "lipids"
serum, *1:* 280, 315, 474; *2:* 145
coagulation, *1:* 71, 403, 445
age, sex, pregnancy, diet, anesthesia, species variation, *1:* 12
prothromboplastin activities, *1:* 291
corpuscular volume, sex variation, *1:* 25
dye concentration
effect of sampling and physical activity, *1:* 214
electrolytes, *1:* 403
see also "solutes"
Ca, Cl, PO_4, *1:* 280
K, Na, P, plasma, *1:* 275
Na, K, Ca, Mg, Cl, PO_4, bicarbonate, in serum, *1:* 434
erythrocytes, *1:* 40, 71, 198, 275, 403, 445
age, sex variation, *1:* 12, 25, 77, 324
central or peripheral vessels, from, *1:* 82
effect
of altitude on, *1:* 228

Dog (*continued*)
of anesthesia, diet, pregnancy, species, on, *1:* 12
of irradiated food on, *2:* 355
of sampling and physical activity on, *1:* 214
life span, *1:* 50
major vessels, in, *1:* 184
normal and diseased, in, *1:* 54
number, size, hemoglobin content, volume; sex variation, *1:* 24
packed cell volume; age, sex variation, *1:* 24, 25, 324
extracellular fluid, *1:* 434
fetal, values, *1:* 324
hematocrit, *1:* 71, 198, 275, 434, 445
effect of sampling and physical activity on, *1:* 214
hemoglobin, *1:* 71, 198, 275
age, pregnancy, diet, anesthesia, species variation, *1:* 12
and sex variation, *1:* 12, 24, 77, 324
effect of irradiated food on, *2:* 355
hemoglobin concentration, sex variation, and, *1:* 25
in mother and young, *3:* 75
in normal and diseased, *1:* 54
sulfhydryl groups in, genetics of, *1:* 392
leukocytes, *1:* 40, 71, 198, 275, 403, 445
age, pregnancy, diet, anesthesia, species variation, *1:* 12
sex variation, *1:* 12, 25, 77, 324
effect of irradiated food on, *2:* 355
in major vessels, *1:* 184
in normal and diseased, *1:* 54
lipid fractions, serum, *1:* 315; *see also* "cholesterol"
lipids, serum, *1:* 403, 412
newborn of; quantitative study, *1:* 60
nitrogenous constituents, *1:* 275, 280, 434
plasma volume, *1:* 49, 434
and available fluid, *1:* 34
effect of transfusion, *1:* 374
proteins, *1:* 275, 280, 299, 412, 434, 506; *2:* 145
albumin, *1:* 403
amino acids, in portal vs. radial; effect of diet on, *1:* 131
effect of sampling and physical activity, on, *1:* 214
effect of transfusion on, *1:* 374
total, and electrophoretic fractions in plasma, age variation, *1:* 65
reticulocytes, *1:* 71, 275
sex variation, *1:* 25
sedimentation rate, *1:* 71, 275, 403, 445
age, sex, lactation, pregnancy variation, *1:* 324
solutes, plasma, in resting hydropenia and in osmotic diuresis, *1:* 92; *see also* "electrolytes"
specific gravity, *1:* 71
age, sex, pregnancy, diet, anesthesia, species variation, *1:* 12
sugar, *1:* 403, 412
see also "metabolism, carbohydrate"
glucose, plasma, *1:* 275, 280
thymol turbidity, plasma, *1:* 275
viscosity, *1:* 403
volume, *1:* 49, 71, 437, 480
age, sex, pregnancy, diet, anesthesia, species variation, *1:* 12
blood flow
in arteries and veins of paw; effect of stimulation on *1:* 442
in bronchial artery, *1:* 435
in hind limbs; effect of cold on, *1:* 250
in normal, sympathectomized, and exposed to cold; effect of drugs on, *1:* 248
blood pressure *1:* 368
arterial and venous, of paw; effect of stimulation on, *1:* 442
breed variation, *1:* 96
pulmonary artery, *1:* 309
vs. adrenal blood flow, *1:* 215
blood types, *1:* 38, 467
genetics, *1:* 129
transfusions, and, *1:* 397
blood vessels, cholesterol biosynthesis in vitro, *1:* 326
body fat, density, *1:* 142
body heat generation, *5:* 22
body temperature
breed variation, *1:* 96
effect of cold on, and, *1:* 154
effect of food deprivation and physical activity on, *1:* 516
muzzle, ear flap, rectum, *1:* 344
pregnancy, in, *4:* 71
body water
balance, *1:* 172
loss; effect of food deprivation and physical activity on, *1:* 516
sodium space, and, *1:* 487
body weight
see also "growth"
effect of irradiated foods on, *2:* 355
bone marrow
cytology, *1:* 51, 54, 74, 153, 403
erythrocytopoiesis vs. granulocytopoiesis in newborn, *1:* 60
books, bibliographies, periodicals, symposia on:
Bibliography of the Dog, *1:* 481
Canine Medicine, *2:* 330
Canine Surgery, *2:* 178
Care of the Dog Used in Medical Research, *5:* 24
Dissection of the Dog, *1:* 113
Dog Research News, *9:* 8
Dog World, *9:* 9
Experimental and Clinical Studies of the Spine of the Dog, *1:* 20
Genetics of the Dog, *4:* 24
Index of Diagnosis for the Canine and Feline Surgeon, *2:* 54
Index of Treatment in Small Animal Practice, *2:* 69
Neoplasms of the Dog, *2:* 25
Neurological Examination of the Dog, *2:* 113
Newer Knowledge about Dogs, *9:* 10
Nutrition of the Dog, *3:* 16
Topographical Anatomy of the Dog, *1:* 428
brain
see also "spinal cord"
blood flow and O_2 consumption, *1:* 424
electroencephalogram, age variation, *1:* 231
digestive tract, fluid volume, *1:* 172
enzymes
amylase, serum, *1:* 412
cholinesterase in blood, *1:* 219, 477; *2:* 316
glutamic oxaloacetic and pyruvic transaminases in serum and tissues, *1:* 439
glutamic transaminase in blood, *2:* 145
phosphatase
alkaline, in blood, *2:* 145
alkaline, in urine, *1:* 275
in blood, *1:* 280
trypsin titer in feces, *2:* 149
eyes
anatomy and physiology, *1:* 260
pupil diameter and contraction; breed variation, *1:* 96
feces, fecal flora, *1:* 246
food consumption, *3:* 34; *5:* 117
seasonal variation, *3:* 21
water consumption, age variation, and; effect of diet on, *3:* 76
food requirements, *3:* 16
adult and young, *3:* 75
caloric, *3:* 30, 44, 56
formula for; variation with age, activity, lactation, pregnancy, *3:* 23
standard values, *3:* 35
genetics, *1:* 481
and behavior patterns, *1:* 144
and blood types, *1:* 129
formulas for, *4:* 24
growth, development, *1:* 234
hair, color, genetics, *4:* 24
heart
atrial pressure, *7:* 47

Dogs (*continued*)
beat and EKG, *2:* 141
blood volume, *1:* 480
electrocardiograms, *1:* 103, 155
function, breed variation, *1:* 96
output, *7:* 169
rate, and effect of cold on, *1:* 154
and emotional reactivity, *1:* 144
respiratory response, and; effect of food deprivation and physical activity, *1:* 516
immune bodies in blood
antigens, isoagglutinins, in blood types, *see* blood types
distemper, measurement of; predicting age for vaccination in newborn, *2:* 230, 293
infectious hepatitis, and; predicting age for vaccination in newborn, *2:* 128
immunology, *1:* 481
kidney
see also "metabolism, carbohydrate; mineral," "urine chemistry"
function *1:* 92
calcium clearance, *1:* 202
effect of altitude on, of polycythemic, *1:* 228
red cell, plasma volumes, hematocrit; effect of hemorrhage on, *1:* 367
liver
cholesterol, *1:* 474
function, *1:* 275; *2:* 145
amino acid excretion in urine in health, disease, estrus, pregnancy, *1:* 356
lung
see also "respiration"
blood volume, *1:* 478, 480
pressure, *1:* 478
metabolism, basal, *3:* 23
oxygen consumption, *1:* 424
and heat production, loss; effect of cold on, *1:* 154
metabolism, carbohydrate
see also "blood sugar"
blood sugar vs. excretion through kidney, *1:* 136
metabolism, mineral
see also "blood electrolytes"
calcium excretion, renal, *1:* 202
nutrition, *1:* 481; *2:* 330
see also "food consumption; requirements"
pain response, *7:* 73
threshold, teeth, *7:* 20
physical activity in
caloric requirements, for, *3:* 23
effect of feeding time on, *1:* 517
effect on spermatogenesis, *1:* 332
physiological response, and, *1:* 214, 516
physiology, book, *1:* 135, 481; *2:* 178, 330
pleural fluid, turnover
volume, proteins, erythrocytes, leukocytes, *1:* 408
reproduction and sex organs, *1:* 353, 438; *5:* 117
estrus
and amino acids excretion in urine, *1:* 356
determination, *4:* 106
fetal fluid, placental type, endometrial differentiation, *1:* 267
lactation and pregnancy, caloric requirements in, *3:* 23
pregnancy, amino acids excretion in urine, *1:* 356
body temperature before and after parturition, diagnostic value, *4:* 71
sexual behavior, breed and environmental variation, *1:* 144
spermatogenesis; effects of diet and exercise on, *1:* 332
respiration, anatomy, mechanics, physiology, *1:* 394
CO_2 in exhaled air, *1:* 435
constants, *7:* 164
intrapleural pressure, *7:* 102
mechanism of, *1:* 495
oxygen consumption, *1:* 154, 309, 424
rate; respiratory minute volume, and effect of cold on, *1:* 154
skin
genetics, *4:* 24
temperature, *1:* 344
skull, radiographs, *2:* 239
sodium space, *1:* 487
spinal fluid
biochemistry and cytology, in health and disease, *1:* 207
pressure, physical and cytological properties, *2:* 183
production, and cerebral blood flow, metabolism, *1:* 424
spine
anatomy, *1:* 20
x-ray, *2:* 329
taste response, to KCl vs. NaCl, etc., *1:* 200
teeth, *1:* 22
tissue fluids, distribution volume, *1:* 166
urine chemistry, *1:* 275
see also "metabolism, carbohydrate; mineral," "kidney"
amino acids excretion, *1:* 356
chlorides, *2:* 202
solutes, in resting hydropenic conditions and during osmotic diuresis, *1:* 92
use
in behavior pattern research, *6:* 28
in blood and liver research, *4:* 28
in cardiovascular disease research, *2:* 215
in nutritional research, *6:* 42
in radiobiologic research, *4:* 100
in research, *1:* 481; *5:* 24
in skin disease tests, *2:* 351
water consumption, *see* "food consumption"
water requirements, and diet, *3:* 86
Domestic animals
see also Animals; Breeding; Diseases; Housing; Mammals; Vertebrates
anatomy, *1:* 355, 438
behavior, *1:* 185
books and pamphlets, bibliographies, periodicals on
see also books on veterinary medicine, physiology, etc., *under* Books
Animal Breeding Abstracts, *9:* 2
Comparative Anatomy, *1:* 355
Environmental Physiology of Farm Animals, *1:* 178
Neoplasms of the Domesticated Mammals, *2:* 88
Physiology of Domestic Animals, *1:* 27
Physiology of Farm Animals, *1:* 185, 457
Reproduction and Artificial Insemination of Domestic Animals, *1:* 353
Reproduction in Domestic Animals, *1:* 438
Reproductive Physiology, *1:* 393
Technique of Postmortem Examination of Domestic Animals, *7:* 100
food requirements, *3:* 40
hair cycles in, *4:* 46
legislation on health of, *6:* 17
nutrition, *1:* 438
physiology, *1:* 27, 438
environmental, *1:* 178, 185
reproduction, *1:* 185, 353, 438, 457
effect of climate, nutrition, *1:* 455
physiology of, *1:* 393
thermoregulation, *1:* 178
water requirements, *1:* 178
Drenching technique for sheep, *7:* 157
Drosophila, *5:* 27; *see also* Insects
Drugs
action of, *see* Pharmacology
administration
see also Feeding devices; Watering devices; Infusion; Injection; Inoculation; Intragastric administration
in water to rats and drinking habits, *3:* 38
to monkey, *5:* 96

Drugs (*continued*)
effect
on activity of mouse, *7:* 49
on activity of rat, *1:* 380
on behavior in monkey, rat, *7:* 155
testing techniques, *see* Pharmacologic techniques
use of animals in, *see* Pharmacologic research, and specific types of research
treatment of disease, dosage and effects, *2:* 172
see also under Diseases, and specific drugs
index of, *2:* 69, 279
Duck
see also Birds; Domestic animals; Poultry
cholinesterase in blood, *1:* 219
hematology, *1:* 71, 445
Dust exposure techniques, *see* Inhalation chambers

Ear chamber techniques, in rabbit, *2:* 315; *7:* 152
Economics of animal colonies, *see* Costs
Ectoparasitism in animals, *see* Diseases, "parasitic, arthropod"
Ectromelia, *2:* 118
Edema measurement, plethysmometric, in mouse, rat, *7:* 95
Edentates, body organ, gland weights, *1:* 37
Eimeria stiedae, *1:* 323; *2:* 313; *4:* 93
Electric shock, induction of, *7:* 168
Electrical stunning of dog, *7:* 4
Electrocardiography
in dog, *1:* 103, 155; *2:* 141, 150
in guinea pig, *7:* 10
in hamster, *1:* 163
in laboratory animals, *7:* 10, 148
in mouse, *7:* 10
in rabbit, *1:* 97
in rat, *7:* 10, 82
Electrocution, *see* Euthanasia
Electroencephalography
in dog, *1:* 231
in rabbit, and recording equipment, *7:* 88
Electron microscopy
of capillaries, morphological classifications, *1:* 423
of reproductive organs, *1:* 340
of tumors, virus-induced, *2:* 228
Electrophoresis, *see* "hemoglobin," "proteins," *under* Blood study techniques, test for rabies, *2:* 76
Encephalitozoon cuniculi, *2:* 249, 290
Endamoeba histolytica, *2:* 352
Endocrinologic research, use of rats in, *4:* 52
Endoparasitism in animals, *see* "parasitic, helminth," *under* Diseases
Energy requirement measurement
in dog, *3:* 30
statistical, *3:* 32
Enterococcus, *2:* 39
Entomology, *2:* 112
Environment
adaptation of laboratory animals to, *5:* 108
biological, *see under* Population dynamics; Diseases ("bacterial," "fungal," etc.); Human contact
dietary requirements, and
of animals, *3:* 33
of mouse, rat, *3:* 46
effect
on disease in wild rat, *2:* 248
on growth and weight of rat, *4:* 29
on reproduction in domestic animals, *1:* 438
on sexual behavior, *1:* 144
on tumor incidence, in rat, *2:* 229
mortality in experimental animals, and, *2:* 299
physical
apparatus for recording choice of, *7:* 12
effect
see also under Humidity; Light; Noise; Temperature; "physical agents" *under* Diseases
of change on rat, *1:* 158
on tumor incidence in rat, *2:* 229
on wild animals, *1:* 85
susceptibility of inbred animals to, *4:* 53
Enzymes
see also "enzymes" *under* specific kind of animal
analytical techniques, cholinesterase, *1:* 477; *2:* 211
trypsin in feces as diagnosis of nonspecific diarrhea in dog, *2:* 149
Eperythrozoon coccoides, *2:* 80, 164, 289
Epizoology of disease, *see* "epizoology" *under* Diseases (*under* specific kind of animal and type of agent of disease)
Eptesicus fuscus, *2:* 220
Equithesin anesthesia, *2:* 321
Ergotamine; effect on milk let-down in rat, *1:* 244
Erysipelothrix rhusiopathiae, *2:* 253
Escherichia coli, *1:* 504; *2:* 61, 328; *3:* 78
Escherichia freundii, *2:* 173, 242
Estrogens, *see* Hormones
Estrus determination
see also under "reproduction and sex organs" *under* specific kind of animal
in guinea pig, *1:* 29
Ethers, *see under* Anesthesia
Euthanasia for laboratory animals, *2:* 68, 69, 353; *5:* 1, 102
see also Humane techniques
electrocution, *7:* 2
methods, *7:* 77
Exercise, *see* "physical activity" *under* specific type of animal; for measurement of, see Physical activity measurement
Experimentation, *see* Animal experimentation; *see also* "use" *under* specific kind and groups of animals
Exposure techniques, *see* Eye exposure methods; Feeding devices; Infection; Inhalation chambers; Injection; Inoculation; Intragastric; Metabolism cages; Skin; etc.
Eye
for diseases, *see under* Diseases; *see also* specific kind of animal for physiology of eyes
exposure methods; goggling technique, in guinea pig, *2:* 180
study technique; vision restriction by contact occluders in monkey, *7:* 174

Farm animals, *see* Domestic animals
Fasciola hepatica, *2:* 188
Fasting, effect of, *see* Food deprivation
Feces
see also Metabolism cages
collection
cage for, *5:* 31
separator for, *7:* 84
examination, *7:* 81
for parasites, *see* "animals" *under* Diseases
measurement
in dog, monkey, mouse, *5:* 69
in rat, *1:* 158; *5:* 69
moisture loss determination, in cattle, rabbit, *1:* 379
Feed, *see* Diets; Food
Feeding
artificial, mechanics of, on basis of sucking behavior, *1:* 318
behavior determination in rodent, *3:* 90
devices and techniques
animals (laboratory), for, *5:* 5, 53, 57, 85, 123, 132
automatic
for drugs, and daily ration, *3:* 7
for dry food, *3:* 3
for cubed diet, *3:* 14
for guinea pig, *3:* 29
hand-feeding
cesarean-born, *3:* 85; *4:* 78
gag for, *3:* 29
syringe for mouse, *3:* 4
intranasal intubation, for cat, *2:* 345
intravenous, of cat, dog, *2:* 133

Feeding (*continued*)
latex nipples, *5:* 123
liquid food mixture, tube, for rat, *3:* 6
metabolism cage, *5:* 41, 124
mouse, *3:* 3, 4, 14, 85; *4:* 13; *5:* 37, 131
pellets, for rat, *3:* 2
rabbit, *3:* 29, 85
domestic, *4:* 58
rat, *3:* 2, 6, 29, 82, 85; *5:* 12, 37
random and inbred; standards, *4:* 109
restraint box, for monkey, *7:* 154
rhythm technique, for rat, *3:* 82
rumen fistula apparatus, for sheep, *7:* 153
subcutaneous, in cat, dog, *2:* 133
viscous food, for rat, *3:* 22
regimen, and eosinophil rhythm in mouse, *1:* 150
time
effect on dog, *1:* 517
for mouse, *4:* 6
Felidae, *2:* 36
Ferret
see also Animals; Mammals; Vertebrates
adrenal glands, adrenocortical secretion, *1:* 125
anatomy, *1:* 39, 135
hematology, *1:* 135
nutrition, *1:* 39
physiology, *1:* 39, 135
use in research, *1:* 39; *4:* 66
Fertility tests in animals, *2:* 47
see also Estrus determination; Pregnancy tests; *see also* "reproduction and sex organs" *under* specific kind of animal
Films
anatomy and physiology of laboratory animals, *1:* 83
Animals in Research, *4:* 82
blood circulation in hamsters (*Hemo ne Magnificent*), *1:* 325
breeding program for disease-free animals, *4:* 70
care of guinea pig, *5:* 125
care of laboratory animals, *5:* 74
establishment and maintenance of disease-free animals, *4:* 70, 82
Film Catalogue, *9:* 20
List of Films and Films of Veterinary Interest, *9:* 14
Technique for Handling Rabbits, *7:* 187
Fish
body, organ, gland weights, *1:* 37
care and management, *5:* 27, 102
carotid body and sinus; anatomy, embryology, physiology, *1:* 322
circulatory system, *1:* 486
eyes
anatomy, physiology, *1:* 260
retinal circulation, *1:* 192
food requirements, standard values, *3:* 35
hematology, *1:* 71
nervous system, *1:* 3
Floor plans of animal houses, *see* "construction design" *under* Housing
Fluothane, *see under* Anesthesia
Food
additives, manufacturers' directory, *2:* 279
see also Dietary additives
analysis, chemical, *7:* 81
animals, for, *see* Diets
consumption
of animals, *see* "food consumption" *under* specific kind and groups of animals
effect of brain damage on, *2:* 84
measurement of, *5:* 69
and tumor growth, *2:* 107
contamination
by estrogens and effects, *see under* Hormones
by insects and mites, control, *2:* 31; *5:* 86, 88
by *Salmonella*, *2:* 40; *3:* 80
deprivation or restriction
effect on dog, *1:* 516
effect on mouse, *1:* 384
effect on rat, *1:* 164, 195, 258, 464
technique, for rat, *3:* 82
protection of, from rats, with fence, *7:* 61
requirements, *see* "food requirements" *under* specific kind and groups of animals
storage, *5:* 75
suppliers, *2:* 279
water supplies, and, handling of, *5:* 18
Fowl, *see* Birds; Chicken; Domestic animals; Duck; Goose; Poultry; Turkey
Fox, *2:* 134; *3:* 35; *4:* 8; *7:* 33
Frog
see also Amphibia; Diseases
behavior pattern; choice of temperature, *7:* 12
bone marrow; cytology, *1:* 403
books on: *Frog, Its Reproduction and Development*, *4:* 20
cholesterol in blood, bile, liver, *1:* 474
development, *4:* 20
eyes, retinal circulation in, *1:* 192
hematology, *1:* 403; *2:* 47
ovulation, *1:* 83
reproduction, *4:* 20
respiration; anatomy, mechanics, physiology, *1:* 394
use for pregnancy tests, *5:* 56
Fungicides; effect on laboratory animals, *2:* 347

Gastric mucosa, blood, densitometric measurement of, *7:* 150
Gastric secretion measurement
in guinea pig, *1:* 117
in rat, *1:* 117; *7:* 79
Genetics
see also under specific kind and groups of animals
books, *1:* 110, 321; *4:* 24
Gentling, *see under* Handling
Geographical environment, effect of, *see under* Temperature
Gerbil, Mongolian, cholesterol in serum, adrenal, liver; use in atherosclerosis research, *1:* 285
Germfree animals
see also Disease-free animals; Pathogen-free animals; for details on anatomy, physiology, etc., *see under* Chicken; Guinea pig; Mouse; Rabbit; Rat
characteristics of, *4:* 112
chicken, *1:* 452, 499, 503, 508, 514; *3:* 78, 83; *4:* 113
determination of germfree status, *1:* 507
equipment and housing for, *4:* 99, 114; *5:* 105, 129
establishment and maintenance of, *4:* 78, 102, 108, 111, 112, 113
guinea pig, *1:* 482, 514; *2:* 352; *3:* 91; *4:* 108, 111, 113
history, *1:* 468
mouse, *1:* 452, 514; *3:* 85, 91; *4:* 95, 113
rabbit, *1:* 514; *3:* 85, 91; *4:* 117
rat, *1:* 370, 452, 475, 503, 508, 514, 515; *2:* 375; *3:* 85, 91; *4:* 78, 95, 104, 113
use in research, *4:* 112; *6:* 55, 60, 69, 78
Gerontology
see also "aging" *under* Diseases
evaluation of changes in animals, *3:* 67
Glucose tolerance tests in mouse, *1:* 191, 341
Goat
see also Animals; Diseases; Domestic animals
adrenal glands; anatomy, histology, *1:* 489
blood
cellular elements, *2:* 47
plasma volume, and, *1:* 49
proteins, serum, *1:* 451, 506
digestive tract, fluid volume, *1:* 172
fetal fluid, placental type, endometrial differentiation, *1:* 267
hair growth, replacement, type, *1:* 99
milk composition, *3:* 42

Goat (*continued*)
use in insecticide tests, *6:* 46
water balance, *1:* 172
Goose, cholinesterase in blood of, *1:* 219
Gorilla, *1:* 88
"Granuloma pouch" technique in rat, *7:* 62
Greyhound, *1:* 49
Griseofulvin
in hair of guinea pig, *2:* 322
toxicity for cat, *2:* 334
use in treatment of ringworm in guinea pig, *2:* 227
Growth measurement techniques
in cat, *3:* 60
in laboratory animals, *3:* 63; *7:* 58
Guinea pig
see also Anesthesia; Animals; Breeding; Diets; Diseases; Handling; Housing; Laboratory Animals; Mammals; Restraint; Rodents: Vertebrates
adrenal gland
anatomy, comparative; histology, *1:* 489
mitotic activity; effect of thyroxine, heat and humidity on, *1:* 31
steroid
excretion in urine, *1:* 106
strain variation, *1:* 484
weight
vs. body weight, *1:* 128
vs. central nervous system weight, length, *1:* 102
anatomy, *1:* 135
of germfree, *4:* 111
bile, cholesterol, *1:* 474
blood
cholesterol, serum, *1:* 474; *see also* "lipids"
coagulation, *1:* 12, 74, 403
effect of trauma on, *2:* 15
prothromboplastin activities, *1:* 291
electrolytes, *1:* 109, 403
erythrocytes, *1:* 71, 101, 403
age variation, *1:* 12, 290
from central or peripheral vessels, *1:* 82
life span vs. bone marrow erythrocytes, *1:* 447
hematocrit, *1:* 71
age variation, *1:* 290
hematology, *2:* 47
of germfree, *4:* 111
variation with age, sex, pregnancy, diet, anesthesia, species, *1:* 12
hemoglobin, *1:* 71, 101
age variation, *1:* 12, 290
hemolysis, *1:* 12
leukocytes, *1:* 71, 101, 403
age variation, *1:* 12, 290
lipids, *1:* 403; *see also* "cholesterol"
platelets, *1:* 101
proteins
albumin, *1:* 403
serum, γ-globulin in conventional and germfree, *1:* 514
reticuloendothelial system, phagocytic activity of, *1:* 279
reticulocytes, *1:* 71
sedimentation rate, *1:* 71, 403
specific gravity, *1:* 12, 71
sugar, *1:* 403
viscosity, *1:* 403
volume, *1:* 12, 71, 222
water, plasma, *1:* 109
blood pressure, arterial, under local or general anesthesia, *1:* 255
blood vessels
capillary resistance; effect of trauma on, *2:* 15
cholesterol biosynthesis in vitro, *1:* 326
body, chemical composition of, age, sex variation, *1:* 89
body fat
concentration, age, sex variation, *1:* 89
density, *1:* 142
body heat production, *5:* 22
in cold; mechanism, *1:* 262
body length
vs. brain and spinal cord weight and length, *1:* 86
vs. endocrine gland weight, *1:* 102
body temperature, *1:* 101
body water balance, *1:* 172
age, sex variation, *1:* 89
body weight, *1:* 189
at birth; growth of young, *4:* 12
ratio of organ weight to, of inbred, *1:* 84
vs. brain weight, *1:* 86
vs. endocrine gland weight, *1:* 102
bone marrow
cytology, *1:* 403
erythrocytes, life span, vs. blood erythrocytes, *1:* 447
hemopoietic elements and composite cellular lines in femur age variation; histology, *1:* 290
nucleated cells in right and left humerus, *1:* 187
volume, distribution of; age variation, *1:* 305
book and bibliography
care of guinea pig in clinical research and sources of supply, *5:* 125
Guinea Pig in Research, *3:* 74
brain
anatomy of basal telencephalic centers; histology, *1:* 308
spinal cord weight vs. endocrine gland weight, *1:* 102
thalamus, nuclear topography and architectonics, *1:* 216
weight of parts, *1:* 86
digestive tract, fluid volume, *1:* 172
gastric juice volume and acidity, *1:* 117
enzymes, transaminases, oxidases, total body activity
body weight and sex variation, *1:* 476
feces, fecal flora, *1:* 246
food consumption, *3:* 34; *5:* 117
food requirements, *3:* 13, 73, 74
caloric, *3:* 56
standard values, *3:* 8, 35
vitamins, effect on reproduction, *3:* 5
growth
effect of diet on, *3:* 62
effect of synthetic vitamin C on, *3:* 25
hair growth, *1:* 366
replacement, type, *1:* 99
heart
rate in pregnancy, *1:* 302
weight vs. body weight in inbred, *1:* 84
histamine in skin, age and weight variation, *1:* 252
immune bodies
antibodies in blood, complement, titer, *1:* 229
antibodies titer against testis in testis-injected, *1:* 465
immunity and serum proteins of conventional and germfree, *1:* 514
kidney weight, vs. body weight of inbred, *1:* 84
life span; effect of ascorbic acid on, *3:* 87
liver
biochemistry vs. body weight, *1:* 221
blood flow in, *1:* 279
cholesterol, fat, protein, minerals, water in; age, sex variation, *1:* 474
weight, *1:* 221
vs. body weight of inbred, *1:* 84
lung
blood volume, early postnatal, *1:* 108
weight, *1:* 189
vs. body weight of inbred, *1:* 84
lymphatic tissue, morphology, *1:* 482
of germfree, effect of *Coccus* monocontamination on, *1:* 482
metabolism, basal, *1:* 66, 221, 371

Guinea pig *(continued)*
oxygen consumption, effects of cold and restraint on, *1:* 419
in pregnancy, *1:* 302
metabolism, fat and mineral
age, sex variation, *1:* 89
metabolism, protein
age, sex variation, *1:* 89
sulfhydryl groups in skin, esophagus, tongue, *1:* 137
muscle, electrolytes and water in, *1:* 109
physiology, *1:* 135; *3:* 74
pituitary gland
cellular changes during reproductive cycle, *1:* 29
-thyroid system activity; effect of cold and heat production, *1:* 262
weight vs. body, central nervous system, weight and length, *1:* 102
pulse rate, *1:* 101
reproduction and sex organs, *5:* 90, 117
effect of diet on, *3:* 5, 57
effect of electroejaculation frequency, *4:* 86
estrus, cyclical changes in uterus, cervix, vagina, sexual skin; histology, *1:* 340
determination of beginning of, *1:* 29
fertility, *1:* 465
fetal fluid, placental type, endometrial differentiation, *1:* 267
gestation, abortions, stillbirths, sterile matings in inbred effect of thyroxine, *1:* 301
time, incidence of abortions, stillbirths in inbred, *1:* 296
lactation; effect of diet, *3:* 62
litter size
effect of ascorbic acid on, *3:* 87
effect of diet, *3:* 62
of inbred; effect of thyroxine, *1:* 301
litters without 2nd breeding, *1:* 139
pregnancy, oxygen consumption, heart rate in, *1:* 302
reproductive cycle and cellular changes in anterior hypophysis, *1:* 29
sexual behavior, effect of undescended testes on, *1:* 272
sterility, induction in, *1:* 465
testes, undescended, effect on internal secretory capacity, *1:* 272
weight vs. body, central nervous system, weight and length, *1:* 102
respiration, *1:* 101
anatomy, mechanics, physiology; tables, *1:* 394
constants, *7:* 164
volume, *1:* 72
skin
histamine, "labile," after death, age and weight variation, *1:* 252
sulfhydryl groups in, *1:* 137
spinal cord, length and weight, *1:* 86
spleen
fat, proteins, water, minerals in; age, sex variation, *1:* 89
weight vs. body weight, of inbred, *1:* 84
taste responses, to KCl vs. NaCl, etc., *1:* 200
thyroid gland
see also under "pituitary gland"
histology; effect of thyroxine, heat and high humidity, *1:* 31
weight vs. body, central nervous system, weight and length, *1:* 102
urine
steroid excretion, *1:* 106
of inbred; strain variation, *1:* 484
use
adrenocorticoid excretion studies, *1:* 106
as assay for pyrogen detection, *6:* 34
for brucellosis vaccine tests, *6:* 16
germfree in amebiasis studies, *2:* 352
for insecticide tests, *6:* 46
for pseudorabies diagnosis, *2:* 256
for rabies diagnosis, *2:* 76
for testing milk, etc., *5:* 40
for tuberculosis test, *5:* 97
water consumption, in normal and irradiated, *3:* 38
water requirements, *5:* 40

Haemobartonella, *2:* 222, 231
Haemobartonella canis, *2:* 296
Haemobartonella muris, and *musculi*, *2:* 289
Hair removal techniques, *7:* 3, 27
Halothane, *see under* Anesthesia
Hamster
see also Animals; Breeding; Diets; Diseases; Handling; Housing; Mammals; Restraint; Rodents; Vertebrates
adrenal glands, weight; effect of pregnancy on brown fat in, *1:* 501
anatomy, *1:* 135
bile, cholesterol, *1:* 474
blood
cholesterol, *1:* 474
coagulation, *1:* 67, 71, 403
electrolytes, *1:* 398
Ca, P, *1:* 67
Mg, *1:* 317
Na, K, *1:* 163
erythrocytes, *1:* 67, 71, 403
from central or peripheral vessels, *1:* 82
hematocrit, *1:* 71
hemoglobin, *1:* 67, 71
leukocytes, *1:* 67, 71, 403
lipids; proteins; albumin, *1:* 403
reticulocytes, *1:* 71
sedimentation rate, *1:* 71, 403
specific gravity, *1:* 71
sugar, *1:* 403
viscosity, *1:* 403
volume, *1:* 71
blood pressure
arterial, cheek pouch, *1:* 201
systolic, *1:* 433
body fat changes in pregnancy, *1:* 501
body water balance, *1:* 172
body weight
see also "growth"
effect of cold and hibernation on, *1:* 360
factors affecting, *3:* 50; *4:* 60
bone marrow, cytology, *1:* 403
circulation, *1:* 325
digestive tract, fluid volume, *1:* 172
enzymes
alkaline phosphatase, adrenal, in pregnancy, *1:* 501
transaminases, oxidases, total body activity vs. body weight, sex, *1:* 476
food consumption, *5:* 117
food requirements, *3:* 13
standard values, *3:* 35
vitamins, *3:* 9
for maintenance and reproduction, *3:* 11
growth, *3:* 11; *4:* 3
and development, *4:* 7
embryonic and to 9th day, *1:* 56
heart, electrocardiogram, *1:* 163
hibernation characteristics and mortality in, *1:* 238
immune bodies, antibodies in blood, complement, titer, *1:* 229
liver
biochemistry vs. body weight, *1:* 221
cholesterol, *1:* 474
function; effect of hibernation and cold, *1:* 460
weight, *1:* 221
metabolism, basal, *1:* 221
nutrition
see also "food consumption," "food requirements"; Diets
weight variation, and, *3:* 50

Hamster (*continued*)
physiology, *1:* 135
reproduction and sex organs, *5:* 90, 117
estrus; effect of cold and hibernation on, *1:* 360
gestation period, *4:* 5
litter size, *4:* 7
maternal age, *1:* 56
pregnancy, brown fat changes during; histology, *1:* 501
pseudopregnancy, period after sterile mating and luteal function, species variation, *1:* 470
reproductive cycle, time table of events, *1:* 267
sexual maturity, gestation, litter size, *4:* 3
vitamin requirements in, *3:* 11
respiratory volume, *1:* 72
taste response, to KCl vs. NaCl, *1:* 200
teeth and gums, eruption and attrition; system for recording, *1:* 156
thymus, brown fat in, weight; effect of pregnancy on, *1:* 501
use
in bacterial disease research, advantages and disadvantages of, *6:* 14
in blood vessel study, *6:* 29
in phlebothrombosis research, *2:* 108
Handling
see also Restraint and protective devices
animals, *7:* 33
birds, caged, *2:* 198
cat, *5:* 38
chicken, *7:* 33
cow, *7:* 33
dog, *7:* 33
effect of, *1:* 363
ferret, *4:* 66
fox, *7:* 33
hamster, *4:* 5
horse, *7:* 33
laboratory animals, *2:* 69; *5:* 1, 79, 90, 102; *7:* 92
code on, *5:* 117
effect of, *1:* 169
gentling, and, effect of, *7:* 94
mink, *7:* 33
monkey, *2:* 30, 97
new arrivals, *2:* 30; *5:* 123
regulations, *6:* 35
mouse, effect of, *1:* 287
poultry, *7:* 33
rabbit, *7:* 33
domestic, *4:* 58
rat, *1:* 45, 87; *5:* 106 (wild)
effect of, *1:* 197; *2:* 309
on thiourea toxicity, *7:* 121
on weaning, *1:* 194
gentling, and, effect of, *1:* 197, 258; *7:* 94, 121
lifting from cages, device for, *5:* 20
squirrel, *5:* 14
swine, *7:* 33
Head holder, *see under* Restraint
Heart
see also Electrocardiography
function tests, *2:* 307
output measurement
in chicken, *1:* 496
in dog, *7:* 169
rate determination
apparatus, for rat, *1:* 70
in guinea pig with radio-I, *1:* 302
Heat, as sexual response, *see* "estrus" *under* "reproduction" *under* specific kind and groups of animals; otherwise, "heat" refers to high temperature
Helminthology, *2:* 112; *see also* "parasitic, helminth" *under* Diseases
Hematology, *see* "blood," "hematology" *under* specific kind and groups of animals
Hemorrhage, effect of, *see* Blood loss
Hibernating mammals, blood electrolytes in, *1:* 317, 398
Hibernation
effect
on hamster, *1:* 238, 360, 460
on marmot, *1:* 122
on rabbit, raccoon, *1:* 292
Histologic techniques, *see* Pathologic techniques
Histoplasma capsulatum, *2:* 220, 315
Holding, *see* Handling
techniques, *see* Restraint and protective devices
Hookworm, *see* "parasitic, helminth" *under* Diseases
Hormel Institute, University of Minnesota, *4:* 35
Hormones
adrenocorticotrophic
effect on mouse, yellow obese, *1:* 341
interpretation of results in rabbit, rat, *1:* 125
assays, *7:* 164
use of mouse in, *2:* 167
use of rat in, *7:* 62
cortisone
effect on mouse, *2:* 39
effect on rat, *1:* 152, 224; *2:* 369
diethylstilbestrol
effect on rat, *3:* 66
tumor incidence in mouse, and, *4:* 101
diets, in, *see* Dietary additives
estrogens
effect on mouse, *1:* 288, 289; *4:* 53
effect on rabbit, *1:* 303
effect on rat, *1:* 378
gonadotropin; effect on mouse, *1:* 293, 295
therapeutic use in animals, *1:* 159; *2:* 304, 332
use in breeding programs, *4:* 75, 84
Horse
see also Anesthesia; Animals; Diseases; Domestic animals; Mammals; Vertebrates
adrenal glands, anatomy, histology, *1:* 489
blood
hematology, *1:* 12, 71; *2:* 47
hemoglobin, sulfhydryl groups in; genetics of, *1:* 392
plasma volume, and, *1:* 49
proteins, serum, *1:* 506
blood pressure, *1:* 368
blood types, *1:* 467
body weight, vs. liver biochemistry, *1:* 221
enzymes, glutamic oxaloacetic and pyruvic transaminases in serum and tissues, *1:* 439
eyes
anatomy, physiology, *1:* 260
retinal circulation, *1:* 192
feces, fecal flora, *1:* 246
fetal fluid, placental type, endometrial differentiation, *1:* 267
food consumption, *3:* 34
food requirements, *3:* 35
immune bodies
antibodies in blood, complement, titer, *1:* 229
antigens in blood, *1:* 467
liver
biochemistry vs. body weight, *1:* 221
function, *2:* 344
weight, *1:* 221
metabolism, basal, *1:* 221
milk composiion, *3:* 42
reproduction, *1:* 438
respiratory constants, *7:* 164
Hospitals
for animals, *1:* 135
for cat, dog, *5:* 25
Housing
see also Cages; Personnel; Quarantine; Sanitation; Sterilization; *see also under* Breeding

Housing (*continued*)
animals, laboratory
see also specific kind of animal below
air, conditioning, *5:* 17, 39, 45, 71, 122
see also "environmental requirements" *under* specific kind and groups of animals listed below; "odor," "ventilation"
disinfection, sterilization, *5:* 83
bacterial, insecticidal aerosols, *5:* 86
detergents, *5:* 100
in disease- and germfree colonies, *4:* 82, 87; *5:* 129
UV light, *5:* 71, 82, 92, 101
purification with activated carbon, *5:* 22
sanitation requirements, *2:* 117
barrier on cage racks
system for disease- or germfree colonies, *5:* 129
UV light for, in infectious disease laboratories, *5:* 101
bedding, *5:* 44, 75, 117, 123
see also Bedding materials
control of mange mites on, *2:* 368
sterilization for disease- and germfree, *4:* 82; *5:* 129
building program, *5:* 29; *see also* "construction design"
care and, *1:* 101, 135, 403; *4:* 45; *5:* 1, 27, 46, 81, 89, 90, 94, 115; *9:* 6, 16
environmental control, and, *5:* 75
in germfree vs. clean colonies, *4:* 78
law on, *6:* 33
rules, *6:* 36
centralized supply facility, *5:* 32
construction design, floor plans, *5:* 17, 18, 36, 39, 44, 68, 72, 73, 77, 85, 115, 122
consultation service, *5:* 126
for disease-, germ-, or pathogen-free, *4:* 82, 85
for radiobiologic research, *5:* 39
specifications, *5:* 21
for small animals, *5:* 70
construction materials, *5:* 70
for disease- or germfree, *4:* 113, 114; *5:* 129
for radiobiologic research, specifications, *5:* 21
for virus research, *5:* 64
costs, *8:* 9, 12
capital and operating, *5:* 102; *8:* 7
equipment, *5:* 8
germfree units, *4:* 113
decentralization of units, advantages of, *5:* 87
disinfectants for germfree colonies, *4:* 114
environment
see also Environment; Humidity; Light; Temperature
effect of, *3:* 33; *5:* 108
environmental requirements, *5:* 1, 57
see also "humidity," "lighting," etc.
for disease-free, *4:* 82
equipment, *5:* 65, 72
see also Cages; Feeding devices; Watering devices
cabinet unit, germfree and virus-proof, *5:* 105
savings in cost of, *5:* 8
sterilization, *5:* 100
in disease-free colony, *4:* 82
for eradication of spirochetal disease, *2:* 280
food, *see* Diets; Food
health hazards to personnel, *8:* 3; *see also under* Personnel
heating, *see* "environmental requirements," "temperature requirements" *under* specific animal
humidity, *5:* 2, 39, 122
see also "environmental requirements"; for effect, *see* Humidity
disease incidence and, *2:* 281
insulation, *5:* 77
lighting, *5:* 122
see also "environmental requirements"
effect on animals, *5:* 108; *see also under* Light
noise
control, *5:* 44, 127
effect on animals, *5:* 108
odor
control, *5:* 58
effect on animals, *5:* 108
free air requirement, *5:* 22
organization, *8:* 9; *see also* Personnel
paints, floor, *5:* 28
pest control
see also "sanitation"
insects, with aerosols and lacquers, *5:* 86
insects, with chemicals, *2:* 31, 45
parasite control and, *5:* 27, 44, 75, 86, 117
rat extermination, *2:* 69
radiobiologic research, *5:* 39, 61, 79, 115
sanitation, *5:* 1, 2, 17, 18, 27, 57, 74, 75, 77, 100, 102, 122, 123
cages, standards, *5:* 30
code on, *5:* 117; *6:* 12
disease- or germfree, *4:* 82; *5:* 123, 129
principles of, *5:* 84
ringworm control, *2:* 246
site for, *5:* 65
space requirements, *5:* 35, 123; *see also* "construction design"
standards, *5:* 30
temperature requirements, *5:* 2, 17, 39, 60, 65, 117, 122, 123
see also "environmental requirements"; *also under* Temperature
disease incidence and, *2:* 281
effect on animals, *1:* 59; *5:* 108; *6:* 37
ventilation, *5:* 17, 60, 65, 72, 77, 117
see also "environmental requirements"
air circulation requirements, *5:* 35
effect on animals, *5:* 108
birds
see also "chicken," "poultry"
care, sanitation, *1:* 135; *5:* 102
cat, *4:* 98; *5:* 34, 38, 76
see also "animals"
care, *1:* 135; *5:* 1
control of infections, *2:* 124
construction design, *5:* 85, 122
environmental requirements, sanitation, *1:* 135; *5:* 2, 57, 122
odor-free air requirements, *5:* 22
space and air circulation requirements, *5:* 35
standards, *6:* 45
sterilization of cages, food, water dishes, *2:* 74
cattle
see also "domestic animals"
brucellosis immunity tests, *6:* 16
isolation for newborn; costs, *5:* 119
temperature requirement, *1:* 307
chicken, *4:* 23; *5:* 76
see also "animals," "dometic animals," "poultry"
construction design, *5:* 122
design and operation of isolator units for germfree; costs, *4:* 113
environmental requirements, *5:* 1, 2, 57, 122
odor-free air requirements, *5:* 22
radiobiologic research, *5:* 79
dog, *4:* 28; *5:* 76
see also "animals," "domestic animals"
cages, *3:* 17
care, *1:* 135; *9:* 9, 10
standards, *6:* 15
construction design, *5:* 85, 122
control of infection, *2:* 124
environmental requirements, *5:* 1, 2, 57, 122
kennels
construction and equipment, *3:* 16; *5:* 23
pen space, sanitation, *4:* 100
prefabricated, *5:* 48
odor-free air requirements, *5:* 22

Housing (*continued*)
radiobiologic research, *5:* 79
sanitation, *1:* 135; *5:* 1, 2, 24, 57, 122
sound-conditioning paint for, *5:* 127
space and air circulation requirements, *5:* 35
standards, *6:* 15, 45
tick eradication, *2:* 105
domestic animals
see also "cattle," etc.
lighting, and effect on breeding, *4:* 46
ferret, *1:* 39; *4:* 66
frog, and care, *5:* 56
guinea pig, *5:* 40, 76
see also "animals"
cages, *5:* 97
care, management, *1:* 135; *5:* 1, 125
and costs, *8:* 12
construction design, *5:* 63, 85, 122
design and operation of isolator units for germfree; costs, *4:* 113
detachable sections instead of cages, *5:* 120
environmental requirements, *5:* 2, 57, 122
and tolerance to high humidity and temperature, *6:* 41
galvanized tubs for, *5:* 93
odor-free air requirement, *5:* 22
radiobiologic research, *5:* 79
sanitation, *1:* 135; *5:* 2, 57, 122, 125
space and air circulation requirements, *5:* 35
temperature requirements, *5:* 28
hamster, *4:* 10, (Chinese) 81
see also "animals"
construction design, *5:* 85, 122
environmental requirements, sanitation, *5:* 2, 57, 122
multiple, *5:* 98
salmonellosis prevention, *2:* 108
space and air circulation requirements, *5:* 35
temperature requirements, *4:* 5, 7
monkey, *5:* 61, 67, 76; *see also* "animals"
care, management, *1:* 13, 135; *5:* 1, 102
of new arrivals, *2:* 30; *5:* 123
records, *8:* 5
construction design, *5:* 85, 122
control of diseases, *2:* 70
environmental requirements, *5:* 2, 57, 122
odor-free air requirements, *5:* 22
radiobiologic research, *5:* 79
sanitation, *1:* 135; *2:* 30; *5:* 2, 57, 67, 96, 104, 122
temperature requirements for captive marmoset, *2:* 168
mouse, *5:* 76
see also "animals"
air conditioning, *5:* 45
care, management, *1:* 44, 135; *5:* 1
and costs, *8:* 12
of *Salmonella*-free; costs, *5:* 121
construction design, *5:* 63, 85, 122
cage arrangement, costs, for inbred, *5:* 113
conventional and germfree, and survival, *4:* 95
design and operation of isolation units for germfree; costs, *4:* 113
environmental requirements, *5:* 2, 45, 57, 122
and disease incidence, *2:* 29
and tolerance for high humidity and temperature, *6:* 41
multiple, *5:* 98
odor-free air requirements, *5:* 22
radiobiologic research, *5:* 79
requirements, *4:* 6
costs, *8:* 1
of inbred and random bred, *4:* 76
sanitation, *1:* 135; *4:* 26; *5:* 2, 45, 57, 122
bedding for control of mange mites, *2:* 368
disease incidence, *2:* 29
space, and air circulation requirements, *5:* 35
disease incidence, *2:* 29
specific-pathogen-free colonies, *5:* 109
standards for inbred and random bred, *4:* 76
temperature requirements, *4:* 13; *5:* 28, 43; *see also* "environmental requirements"
in hot climates, *4:* 6
opossum, and care, *5:* 128
pigeon, and care, *1:* 311; *see also* "birds"
poultry, *5:* 49
see also "birds," "chicken," "domestic animals"
care, *5:* 1
lighting, and effect on breeding, *4:* 46
rabbit, *5:* 76, 110
see also "animals"
breeding units, *5:* 78
care, *1:* 135; *5:* 1
and costs, *8:* 12
of domestic, *2:* 135; *4:* 58
construction design, *5:* 63, 85, 122
detachable sections instead of cages for, *5:* 120
environmental requirements, *2:* 135; *5:* 2, 57, 122
odor-free air requirement, *5:* 22
radiobiologic research, *5:* 79
sanitation, *2:* 135; *4:* 115; *5:* 2, 57, 110, 122
space and air circulation requirements, *5:* 35
temperature requirements, *1:* 307; *5:* 28
rat, *1:* 87; *5:* 76; *see also* "animals"
air conditioning, *5:* 12, 45, 122; *see also* "environmental requirements"
bedding, *5:* 12
effect on growth and reproduction, *3:* 62
standards for random and inbred, *4:* 109
care, *1:* 135; *5:* 1
of brown and wild, *5:* 106
construction design, *5:* 63, 85, 122
and cages, *4:* 2
conventional and germfree, and survival, *4:* 95
design and operation of isolator units for germfree; costs, *4:* 113
effects of practices on ringworm infections, *2:* 309
environmental requirements, *5:* 2, 12, 45, 57, 122
and tolerance for high humidity and temperatures, *6:* 41
humidity and disease incidence, *see under* Humidity
multiple, *5:* 98
odor-free air requirements, *5:* 22
pathogen-free colonies, *5:* 109
radiobiologic research, *5:* 79
recommendations for optimum, *5:* 91
sanitation, *1:* 135; *5:* 12, 57
standards, *6:* 19
for random and inbred, *4:* 109
space and air circulation requirements, *5:* 35
temperature requirements, *5:* 28
swine, and care, *2:* 219
turtle, *5:* 99
Human contact, and behavior in dog, *1:* 144
Humane techniques, *7:* 92, 99, 109; *8:* 16
see also Anesthesia; Euthanasia; Handling; Restraint and protective devices and techniques
anticruelty laws, *6:* 63
in Gt. Britain, *6:* 10, 47
antivivisection, *5:* 90; *7:* 172
history and regulation, Gt. Britain, *6:* 10
use of impounded dogs, *6:* 20, 31, 32
Humidity
see also Environment; for requirement in housing, *see under* Housing
choice by insects; recording technique, *7:* 12
effect
on animals, *1:* 6; *5:* 108
on dog, *3:* 21

Humidity (*ontinued*)
on guinea pig, *1:* 31; *6:* 41
on mouse, *1:* 16, 23, 36; *6:* 41
on rat, and diseases in, *2:* 216, 281, 301, 319; *4:* 77; *6:* 41
Hymenolepis nana, *2:* 349
Hymenolepis spp., *2:* 190
Hyperventilation technique, *7:* 91
Hypophysectomy, effect on rat, *1:* 121; *2:* 369

Immunology, *1:* 229; *6:* 55
see also Body defense; Serologic techniques; "vaccination" *under* Diseases; for natural immunity in animals, *see also* "immune bodies" *under* specific kind of animal
immunization techniques in fungal infection in guinea pig, *2:* 335
immuno-electrophoretic characteristics of mouse serums, *1:* 461
Implantation techniques
of carcinogenic pellets, *7:* 114
of tissue, subcutaneous, *7:* 78
of tumors, *2:* 107
Inbred animals, *see* "inbred" *under* Laboratory animals; "inbreeding" *under* Breeding; *also* "inbred" *under* specific kind of animal
Infection technique, in mouse, *2:* 164; *7:* 122
see also Inoculation
Infectious disease laboratories, *see* Microbiologic research; for disease in animals, *see under* Diseases
Infusion techniques
see also Injection; Perfusion
flexible needle for i.v. therapy, *7:* 135
into organs and tissues of salamander; apparatus for continuous, *7:* 71
intravenous in
dog; continuous, *7:* 106, 129
laboratory animals, 6 or more, at constant rate, *7:* 171
mouse, *7:* 134
rabbit; prolonged and repeated, *7:* 37
rat, *1:* 217; *7:* 184
Inhalation techniques
for use in anesthesia, *see under* Anesthesia
chambers, *7:* 193
circular, *7:* 43
for constant flow of gases, volatile liquids, *7:* 90
for dusts, for dogs, *7:* 28
hexagonal type, for dog, monkey, rat, *7:* 137
for radiobiologic research, *7:* 43, 147
exposure
aerosol apparatus for guinea pig, *7:* 32
for goat, sheep, swine, *7:* 83
research, *7:* 193
Injection techniques, *1:* 135
see also Implantation; Infusion; Inoculation; Perfusion
intra-arterial, in rabbit, *7:* 42
intracardiac, in newborn mouse, rat, *7:* 127
intracarotid, in rat, *1:* 225
intracerebral
bone drilling device for, in monkey, *7:* 65
instrument, for laboratory animals, *7:* 11
intramuscular, in captive wild animals, equipment for, *2:* 372
intratracheal
in rat, and restraint device for repeated, *7:* 59
in small animals, with laryngoscopic speculum, *7:* 128
intravascular, in newborn mouse, rat, *7:* 127
intravenous
in chick embryo, *7:* 51
in chicken; venipuncture, *7:* 126
in dog; cannulation, *1:* 131
in mouse; holder for, *7:* 13
in rat; cage for continuous and intermittent, *7:* 24
in small animals; holder for, *7:* 14
subcutaneous, in rat
"granuloma pouch," *7:* 62
"pneumoderma pouch," *7:* 115
Injuries in animals, *see* "physical agents" *under* Diseases
Inoculation techniques, *1:* 101, 229
in chicken, *1:* 17
in ferret, *1:* 39
in mouse, *5:* 11
intra-oral, *7:* 122
vs. intranasal; efficiency compared using radioisotopes, *7:* 123
Insecticide tests, use of animals in, *6:* 46
Insecticides, *see* Pesticides
Insectivores
body, organ, gland weights, *1:* 37
care and management, *5:* 102
Insects
see also "parasitic, arthropod" *under* Diseases
behavior patterns
choice of moisture, *7:* 12
feeding, *3:* 77
book on, *2:* 112
circulatory system, *1:* 486
food consumption and feeding behavior, *3:* 77
nervous system, *1:* 3
Institute of Laboratory Animal Resources
dog shipping standards, *6:* 59
history and purposes of, *6:* 19
publication by, *9:* 13, 17; *see also* Author Index *under* National Research Council
Insulin assay, use of mouse in; effect of environment on response, *1:* 498
International Committee on Laboratory Animals
organization, *6:* 39
publication by, *9:* 11
Intracranial administration of carcinogenic pellets, *7:* 114
Intradermal sarcocystin test, *2:* 127
Intragastric administration technique, in mouse, *1:* 479; *see also* Feeding
Intranasal intubation technique, in cat, *2:* 345
Intrapleural pressure measurement, in dog, *7:* 102
Invertebrates
behavior patterns in snail; choice of light, *7:* 12
body, organ, gland weights, *1:* 37
care and management of, *5:* 102
culture methods for, *4:* 4
Ionography, *see* Electrophoresis
Irradiated foods, *2:* 355; *see also under* Diets
Iso-immunization research, use of rabbit in, *1:* 232
Isolation of animals for virus research, *5:* 64; *see also* Quarantine; for cages, *see under* Cages; for effect of, *see under* Population dynamics

JHM virus, *2:* 260
Jiggle cage for activity measurement, *7:* 188

Kidney function tests, *7:* 81
see also "kidney" *under* specific kind and groups of animals
dog, *2:* 202
radiopaque technique, *2:* 307
rat, *7:* 45
Killing of animals, methods for, *see* Electrocution; Euthanasia; Humane techniques
Klebsiella pneumoniae, *2:* 156
Klossiella cobayae, *2:* 210
Kymographic techniques for small animals, *7:* 75

Laboratory animals
see also specific kind of animal; Animals; Breeding; Diseases; Handling; Housing; etc.
anatomy, *1:* 135
biological data on, *1:* 256
blood

Laboratory animals (*continued*)
chemical composition and physical properties; tables, *1:* 486
hematology, *1:* 135
blood flow, *1:* 486
blood pressure; tables, *1:* 486
blood volumes, *1:* 486
books, pamphlets, bibliographies, conferences, periodicals on, *see also* specific kind of animal; Animals; Domestic animals, etc.
Animal Care Panel, Proceedings of, *9:* 18
Animal Colony Maintenance, *5:* 19
Animals for Research, a Catalog of Commercial Sources, *6:* 45
Animaux de Laboratoire: Anatomie, Particularités Physiologiques Hématologie, Maladies Naturelles, *1:* 135
Basic Care of Experimental Animals, *5:* 1
Blutmorphologie der Laboratoriumstiere, *1:* 403
Bulletin of the National Society for Medical Research, *9:* 5
Care and Breeding of Laboratory Animals, *5:* 27
Care and Feeding of Laboratory Animals, *5:* 57
Care of Laboratory Animals, *5:* 75
Care of Laboratory Animals, Practical Guide on the, *5:* 117
Care and Management of Laboratory Animals, *5:* 123
Carworth Quarterly Letter, *9:* 6
Continuing Inventory of Non-Committed Laboratory Animal Stocks, *9:* 17
Communicable Diseases of Laboratory Animals, Notes on, *2:* 27
Design of Animal Houses, *5:* 68
Establishment and Maintenance of a Disease-free Animal Colony, *4:* 82
Experimental Surgery, *7:* 172
Exposure Chambers for Research in Animal Inhalation, *7:* 193
Germfree Vertebrates, Present Status, *4:* 112
Geschwülste der Laboratoriumsnagetiere, *2:* 221
Haltung und Zucht von Versuchstieren, *5:* 81
Humane Experimental Technique, the Principles of, *8:* 16
Humane Technique in the Laboratory, *7:* 107
ICLA Bulletin, *9:* 11
Infections in Laboratory Animals, *2:* 111
Infectious Diseases in Rodents, *2:* 197
Information on Laboratory Animals for Research, *9:* 13
Journal of the Animal Technicians Association, *9:* 16
Laboratory Animals, Handbook of, *4:* 45
Nutrition of Laboratory Animals, *3:* 54
Organization and Administration of an Animal Division, *8:* 10
Pathologie der Laboratoriumstiere, *2:* 207
Planning your Animal Hospital, *5:* 25
Praktische Tierpflege für Naturfreunde und Forscher, *5:* 46
Restraint of Animals, *7:* 33
Tumeurs Spontanées des Animaux de Laboratoire, *2:* 65
U.F.A.W. Handbook on Care and Management of Laboratory Animals, *5:* 102
business in U.S.A., *5:* 102
circulatory system
anatomy, *1:* 486
effect of drugs, chemical substances, diseases, acceleration, compression, decompression on, *1:* 486
films on, *1:* 83
food consumption, *5:* 117
effect of brain damage on, *2:* 84
food requirements, *1:* 256; *3:* 31, 40
minerals, proteins, vitamins, *2:* 144
vs. environmental factors, *3:* 33
genetics, *4:* 64; *5:* 90; *6:* 30
obesity; mechanism and reproduction, *2:* 84
physiologic characteristics, *1:* 220
standards, *4:* 45
germfree
see also Germfree animals
vs. disease, pathogen-free, cesarean-derived, clean; definitions, *4:* 105
growth and development; effect of temperature on, *1:* 59
heart
electrocardiogram, *1:* 486
output, rate, sounds, murmurs, *1:* 486
inbred
see also "inbreeding" *under* Breeding; *see also* "inbred" *under* specific kind of animal
qualities required, *4:* 25
strains, list of, *6:* 39
use in research vs. genetically varied strains, *1:* 220
legal protection, book, *5:* 102
life history and care, *5:* 46
life span; effect of temperature on, *1:* 59
lymph flow, *1:* 486
mental functions; effect of temperature on, *1:* 59
metabolism, basal and carbohydrate; effect of temperature on, *1:* 59
nutrition, *3:* 54; *4:* 45
vs. environment, stress factors, *3:* 33
pain thresholds, *1:* 278
pathogen-free, *see* Disease-free aimals; Pathogen-free animals; Germfree animals
pathology, *2:* 207
physiology, *1:* 135
reproduction and sex organs, *1:* 256
see also Breeding
breeding data, *5:* 123
infertility, causes of, *1:* 169
physiology, *1:* 393
pregnancy, circulatory system in, *1:* 486
sexual functions, fertility; effect of temperature on, *1:* 59
sources of, *see* Sources of supply
use of, *1:* 135; *4:* 45; *5:* 87, 89, 102; *6:* 30; *7:* 92; *9:* 6
establishing threshold limits, in, *6:* 61
history, *6:* 63
legislation on, in Gt. Britain, *6:* 10
licensing, in Gt. Britain, *6:* 47
or replacement by insentient material, *8:* 16
research, disease, and selection of, *6:* 30
metabolic, by radioisotope techniques, *7:* 140
radiobiologic, *6:* 56
selection, care, techniques, *6:* 22
vs. substitutes for animals, *7:* 107
selection of animals for, *6:* 22, 23, 30
by students and science clubs, legal and ethical factors of, *6:* 63
users, categories of, *4:* 40
certification of, in California, *6:* 33
world list of, *6:* 39
Laboratory Animal Breeders, organization, *6:* 57
Laboratory Animals Bureau, Gt. Britain
activities, *6:* 25; *8:* 16
history, *6:* 25
organization, *5:* 102
Lactation, effect of, *see* "reproduction" *under* specific kind of animal
Lactobacillus lactis, *3:* 78
Lagomorphs
see also Rabbit
care and management of, *5:* 102
Lead arsenate in control of tapeworms, *2:* 31
Learning in animals, *see* "behavior patterns" *under* specific kind and groups of animals
Legal aspects of animal experimentation, *8:* 16
Legislation on
see also Regulations
animal care, California, *6:* 27, 33
animal experimentation, Gt. Britain, *6:* 10, 25
animal health, U.S.; survey, *6:* 17
animals, *2:* 353
dog, certification of incoming, U.S., *6:* 17
ordinance, Baltimore, *6:* 32
pound laws, ordinance

Legislation (*continued*)
Michigan, *5:* 24
Oklahoma, *6:* 63
rabbit, *1:* 263
vaccination laws, U.S., *6:* 17
vivisection, *6:* 63
Leptospira australia, *2:* 270
Leptospira ballum, *2:* 280, 371
Leptospira biflexa, *2:* 270
Leptospira canicola, *2:* 195, 292
Leptospira icterohaemorrhagiae, *2:* 195, 292
Leptospira pomona, *2:* 195, 292
Lice (pediculosis), *see* "parasitic, arthropod" *under* Diseases
Lifting device for rat, *5:* 20
Light
see also Environment; Ultraviolet light; for requirements in colonies, *see* "environmental requirements" *under* Housing
choice by mouse, snail; recording technique, *7:* 12
effect on
animals, *1:* 6, 19, 169; *5:* 108
birds, *1:* 9, 140
chicken, *1:* 342
domestic animals, *1:* 455; *4:* 46
ferret, *4:* 66
hamster, *3:* 50
mouse, *1:* 10, 150, 281, 498; *7:* 167
poultry, *4:* 46
rat, *1:* 41, 105, 132; *4:* 16, 22, 32
Lilly Co., Eli, animal supply department, *5:* 32
Lindane
in control of arthropods, *2:* 268
toxicity for mouse, *2:* 368
Lipids measurement in blood by electrophoresis, *1:* 315
Listerella, *2:* 116
Liver
biochemistry vs. species, body size, *1:* 221
biopsy techniques, in dog, *7:* 186
damage determination, *1:* 356; *2:* 313
function tests, *2:* 145; *7:* 81
see also "liver" *under* specific kind of animal
in cattle, *2:* 209
in dog, *2:* 145, 316
in hamster, *1:* 460
in horse, *2:* 344
radioisotope technique, *2:* 307
physiology research, use of dog in, *4:* 28
Livestock, *see* Domestic animals
Locomotion, *see* Physical activity
Longevity, *see* "lifespan" *under* specific kind and groups of animals
Lung
diseases, *see* "respiratory" *under* Diseases
edema measurement technique, *1:* 189
function, *see* Respiration
resection; effect on dog, *1:* 309
Lymph collection techniques, in mouse, *1:* 405
in rat, *7:* 24, 25

Macaca mulatta, *see* Monkey
Macaca philippinensis, *2:* 158, 165
Maintenance of animals, *see* Diets; Housing; Personnel
Malathion
in control of parasites, *2:* 105
toxicity for
birds, cat, *2:* 89
mouse, *2:* 368
Mammals
see also Animals, etc.
adrenal gland weight vs. body weight of wild; statistical analysis, *1:* 128
anatomy, *1:* 112
behavior, sucking; mechanism, *1:* 318
books, bibliographies on
Bibliography of References to Diseases in Wild Mammals and Birds, *2:* 81
Disease in Captive Wild Mammals and Birds, *2:* 2
Functional Anatomy of the Mammal, *1:* 112
Neoplasms of the Domesticated Mammals, *2:* 88
Patterns of Mammalian Reproduction, *1:* 61
blood, coagulation, prothromboplastin activities, species specificity, *1:* 291
body weight, *1:* 37
vs. adrenal weight, *1:* 128
carotid body, sinus; anatomy, macro- and microscopic; embryology, physiology, *1:* 322
development, *1:* 267
gland weight, *1:* 37
hair, growth, replacement and type, *1:* 99
lifespan of wild, *2:* 81
milk, composition of, *1:* 268
nervous system, *1:* 21
nutrition of wild, *2:* 81
organs, and tissues, physiologic interrelations, *1:* 80
weight, *1:* 37
physiologic constitutions, interrelations of, *1:* 80
physiology of wild, *2:* 81
reproduction, *1:* 61, 83
fertilization, *1:* 274
and fertility, mechanisms of, *1:* 123
sucking behavior, mechanics of, *1:* 318
wild, *1:* 128; *2:* 2, 81
Mammary gland growth measurement, *1:* 431, 454
Mange (mites), *see* "parasitic, arthropod" *under* Diseases
Marking techniques for
dog, tattooing, *6:* 54
laboratory animals, *1:* 101, 135; *5:* 1; *6:* 8
for growth determination, *7:* 58
monkey, *5:* 96
tattooing, *6:* 5
hazards of, *2:* 193
mouse, *1:* 44
ear punch for, *6:* 38
numerical system, *6:* 9
rabbit, domestic, *4:* 58
tattooing, *6:* 2, 5
rat, *1:* 87; *4:* 2
ear punch for, *6:* 38
numerical system, *6:* 6, 9
tattooing, *6:* 7
squirrel, *5:* 14
Marmoset, *2:* 168
Marmot, erythrocyte life span; effect of temperature and hibernation on, *1:* 122
Marsupials, care and management of, *5:* 102
Mastomys coucha, *2:* 176
Medical research, use of animals in, *see under* specific type of research, and specific kind of animal; Laboratory animals
Melopsittacus undulatus, *2:* 287, 321
Mental activity, *see* "behavior patterns" *under* specific kind and groups of animals
Metabolic activity measurement, *7:* 86
Metabolism, basal, measurement in
see also under specific kind and groups of animals
cattle; heat production, *1:* 379
dog, mask for, *7:* 7
mouse, apparatus and method, *1:* 126
rabbit; heat production, *1:* 379
rat, *1:* 161
apparatus and method, *1:* 126
small animals, *1:* 371, 429; *7:* 160
apparatus and method, *1:* 64, 126, 276
Metabolism cages, chambers
see also Feces collection, Urine collection
cat, *5:* 103
cost, *5:* 7

Metabolism cages, chambers (*continued*)
cattle, for radioisotope research, *7:* 31
dog, *5:* 26, 50, 55, 69
cost, *5:* 7
goats, *7:* 83
miniature pig, research, decontamination, *5:* 130
monkey, *5:* 69
mouse, *5:* 11, 69
rabbit, cost, *5:* 7
rat, *5:* 10, 16, 69
feces, urine separator, and, *5:* 3, 107
glass, *5:* 41
and urine, feces separator, *5:* 124
N balance determination, *1:* 265
S balance determination, *1:* 414
small animals, *5:* 42, 66; *7:* 160
for radioisotope research, *5:* 47
sheep, *7:* 83
for radioisotope research, *7:* 31
specifications for, *5:* 59
swine, *7:* 83
for radioisotope research, *5:* 130; *7:* 31
wire basket, *5:* 51
Metabolism research, use of germfree rats in, *1:* 475
Methoxychlor, in control of arthropods, *2:* 268
Methylene blue, in treatment of disease, *2:* 103
Microbiologic research
air sterilization in, *5:* 82, 101
cages for, *5:* 54
housing for, *5:* 64
laboratory disinfection in, *2:* 331
use of animals in, *2:* 80; *6:* 14, 62
Micrococcus pyogenes, *2:* 326
Microfilaria, *2:* 359
Microorganisms
physiology, *1:* 316
use in nutrition work, *7:* 107
Microsporum canis, *2:* 227, 323, 334
Microsporum epidermidis, *4:* 95
Microsporum gypseum, *2:* 247
Microsporum quinckeanum, *2:* 134
Microtus agretis, *1:* 10
Milk collection techniques, *1:* 26, 244
Mink
blood, morphology, *2:* 47
food requirements, *3:* 35
handling of, *7:* 33
Mites (mange), *see* "parasitic, arthropod" *under* Diseases
Models vs. animals in experimentation, *7:* 107
Molds, characteristics of, *2:* 114
Monkey
see also Anesthesia; Animals; Baboon; Breeding; Diets; Diseases; Handling; Housing; Mammals; Restraint; Vertebrates; (unless otherwise specified, reference is to rhesus monkey)
adrenal glands; adrenocortical secretion, species variation, *1:* 125
anatomy, *1:* 13, 43, 135
of gorilla, *1:* 88
behavior patterns, *1:* 43
effect of drugs on, *7:* 155
learning in food-sharing tests, *7:* 173
species variation, *1:* 399
vs. population dynamics, *1:* 107
bile, cholesterol, *1:* 474
blood
coagulation, *1:* 12, 32, 71, 383, 403, 445
electrolytes, *1:* 403
erythrocytes, *1:* 12, 32, 71, 383, 403, 445
effect of bleeding on, *2:* 175
of spayed female; effect of stress on, *1:* 40
hematocrit, *1:* 32, 71, 383, 445
effect of bleeding on, *2:* 175
hemoglobin, *1:* 12, 32, 71, 383; *2:* 70
effect of bleeding on, *2:* 175
hemolysis, *1:* 12
leukocytes, *1:* 12, 32, 40, 71, 383, 403, 445; *2:* 70
effect of bleeding on, *2:* 175
spayed female; effect of stress on, *1:* 40
lipids, *1:* 403
cholesterol, *1:* 474
picture; variation with age, sex, pregnancy, diet, anesthesia, species, *1:* 12
platelets, *1:* 383
proteins, albumin, *1:* 403
reticulocytes, *1:* 71, 383
effect of bleeding on, *2:* 175
sedimentation rate, *1:* 71, 383, 403, 445
specific gravity, *1:* 12, 71
sugar, *1:* 403
viscosity, *1:* 403
volume, *1:* 12, 71
effect of bleeding on, *2:* 175
body heat generation, *5:* 22
body temperature; effect of heat and restraint on, *1:* 362
body weight, *1:* 37
bone marrow, cytology, *1:* 403
books, bibliographies on
Anatomy of the Gorilla, *1:* 88
Anatomy of the Rhesus Monkey, *1:* 13
Bibliographia Primatologica, *1:* 43
Bibliography of Primate Malaria, *2:* 14
Diseases of Laboratory Primates, *2:* 360
Primate Thalamus, *1:* 33
brain, thalamus, anatomy, *1:* 33
embryology, *1:* 43
eyes, anatomy and physiology, *1:* 260
food consumption, *3:* 34; *5:* 117
food requirements
caloric, *3:* 56
standard values, *3:* 35
gland weight, *1:* 37
heart rate; effect of heat and restraint on, *1:* 362
liver, cholesterol, *1:* 474
organ weight, *1:* 37
physiology, *1:* 43
reproduction and sex organs, *5:* 90
effect of UV light on captive marmoset, *2:* 168
gestation period and twinning rate of chimpanzee, *1:* 490
parturition, (film), *1:* 83
respiration
anatomy, mechanics, physiology, *1:* 394
volume, *1:* 72
use, in research, *2:* 97
Morphine; effect on dog, *2:* 314
Mortality in animals, *see under* Diseases
Mount Sinai Hospital, animal quarters, *5:* 63
Mouse
see also Anesthesia; Animals; Breeding; Diets; Diseases; Handling; Housing; Mammals; Restraint; Rodents; Vertebrates
adrenal glands, accessory cortical nodules, of inbred and hybrids; age, sex, strain variation, *1:* 375
ascorbic acid content of inbred, sex variation, *1:* 297
function of inbred, *7:* 167
weight
effect of scarring on, *2:* 305
effect of stresses on, *1:* 203
of inbred, sex variation, *1:* 297
vs. population size, *1:* 204
vs. social rank of wild strain "house"; effect of handling on, *1:* 287
alopecia mutation in, *1:* 208
anatomy, *1:* 135, 350
genetics, *1:* 110

Mouse (*continued*)
of multimammate, *1:* 350
of reticular tissue, normal and pathologic, *1:* 174
behavior pattern, *4:* 26
abnormal, *1:* 319
aggressiveness; effect of isolation on, *1:* 416
choice of light, darkness, *7:* 12
effect of isolation, grouping on, *2:* 214
fighting, induction of, *7:* 191
injury and adrenal weight relationship, *2:* 305
of inbred; learning, strain variation, *1:* 444
strain variation, *1:* 407
response to solitary confinement, *1:* 253
social reactions, in males, strain variation, *1:* 226
social rank of "wild strain" house; effect on adrenal weight, *1:* 287
vs. population dynamics, *1:* 107
bile, cholesterol, *1:* 474
biology of inbred and hybrid, *1:* 44
blood, coagulation, *1:* 12, 71, 403
electrolytes, *1:* 403
eosinophil rhythm, sex, strain variation; effect of light, feeding on, *1:* 150
eosinophils, of inbred
see also "leukocytes"
in pregnancy and after delivery, *1:* 149
sex variation, *1:* 297
erythrocytes, *1:* 12, 71, 101, 403
from central or peripheral vessels, *1:* 82
of inbred, strain variation, *1:* 104
granulocytes of inbred, strain variation, *1:* 104; *see also* "leukocytes"
hematocrit, *1:* 71, 450
strain variation, *1:* 104
hemoglobin, *1:* 12, 71, 101
of inbred, age, diet, strain variation, *1:* 28, 104, 400, 401
pattern of, strain variation, *1:* 415
leukocytes, *1:* 5, 12, 71, 101, 133, 403
see also "eosinophils," "granulocytes," "lymphocytes"
of inbred, and strain variation, *1:* 104, 124
tail and heart blood, from, *1:* 180
lipids, *1:* 403
cholesterol, *1:* 474; *2:* 200
of inbred and obese, *1:* 418
of yellow obese, and resistance to cold, *1:* 341
lymphocytes, response to stress, *1:* 133; *see also* "leukocytes"
pH of inbred, strain variation, *1:* 513
picture; variation with age, sex, pregnancy, diet, anesthesia, species, *1:* 12
plasma volume, *1:* 450
of inbred, *1:* 210
platelets, *1:* 101
protein-bound I, plasma, *2:* 200
proteins, albumin, *1:* 403
γ-globulins, serum, of conventional and germfree, *1:* 514
plasma, of inbred; sex, strain variation, *1:* 304
reticulocytes, *1:* 71
strain variation, *1:* 104
reticuloendothelial system, phagocytic activity of, *1:* 279
sedimentation rate, *1:* 71, 403
specific gravity, *1:* 12, 71
sugar, *1:* 403
glucose, plasma, *2:* 200
in yellow obese; resistance to cold, *1:* 341
sulfhydryl compounds, nonprotein; effect of cold, restraint on, *1:* 120
viscosity, *1:* 403
volume, *1:* 12, 71
weight, *1:* 90
blood vessels, capillaries, morphological classification, *1:* 423
body, chemical composition, age, sex variation, *1:* 89
body fat, *1:* 164
age, sex variation, *1:* 89
body heat production, *1:* 126; *5:* 22
body length
effect of temperature on; age variation, *1:* 16
in yellow obese, and resistance to cold, *1:* 341
body temperature, *1:* 101
effect of heat on, *1:* 47
heat loss; effect of environmental temperature, humidity on, *1:* 36
of inbred
effect of cold, restraint, anesthesia on, *1:* 119
rhythms; effect of blindness on, *1:* 182
tail vs. rectum, *2:* 155
body water, *1:* 164, 172
age, sex variation, *1:* 89
body weight, *1:* 164
effect
of estrogens on, *1:* 288
of olfactory bulb removal on, *2:* 125
of stress on, *1:* 203
of temperature on, *1:* 330
age variation, *1:* 16
estrus and pseudopregnancy, *1:* 289
of yellow obese, and resistance to cold, *1:* 341
of young; effect of temperature on, *1:* 116
bone marrow
cytology, *1:* 174, 403
leukocytes, differential, *1:* 5
books, bibliographies, periodicals on
Annotated Catalogue of Mutant Genes of the House Mouse, *1:* 245
Behavior Studies on Inbred Mice, Selected Bibliography, *1:* 407
Biology of the Laboratory Mouse, *1:* 44
Genetics of the Mouse, *1:* 110
Inbred Strains of Mice (periodical), *9:* 12
Mammary Tumors in Mice, *2:* 16
Mouse News Letter, *9:* 15
Production of Inbred Mice, *4:* 65
Supply Bulletin, *9:* 19
brain chemistry, ammonia concentration, *1:* 485
digestive tract, fluid volume, *1:* 172
intestine, hematocrit, *1:* 450
plasma volume, *1:* 210
stomach, capacity, distensibility, age variation, *1:* 479
weight, *1:* 90
embryo, development *in vitro*, *4:* 94
embryology, *1:* 44
enzymes
of inbred, transaminases and oxidases, activity, total body weight, sex variation, *1:* 476
succinoxidase, malic dehydrogenase in heart, kidney, liver, brain, body size variation, *1:* 143
eyes, anatomy, physiology, *1:* 260
food consumption, *2:* 200; *3:* 14, 34, 81; *4:* 13; *5:* 117
food requirements, *3:* 13, 46
caloric, *3:* 56
of growing, *3:* 14
standard values, *3:* 35
genetics, *1:* 44, 110
developmental homeostasis, *1:* 283
growth variability of inbred, *6:* 4
hair loss, *1:* 208
learning ability, in inbred; strain variation, *1:* 444
mutant genes of house mouse, *1:* 245
skeletal types of inbred, *1:* 181
in sublines of inbred, *1:* 148
growth, and development
effect of diet on, *3:* 14, 62
effect of temperature on, *1:* 330
age variation, *1:* 16
humidity, and, *1:* 36
of inbred strain variation, *1:* 283; *6:* 4

Mouse (*continued*)
hair growth, *1:* 171, 366
in alopecia mutation, *1:* 208
patterns in naked, *1:* 193
replacement, type, *1:* 99
Harderian glands, iodine uptake; effect of temperature on, *1:* 298
heart, weight, *1:* 90
immune bodies, antibodies in blood, complement, titer, *1:* 229
immunophoretic characteristics of serum, *1:* 461
immunity
against encephalomyelitis, *2:* 251
auto-immunization after burns, *7:* 181
serum proteins, and, of conventional and germfree, *1:* 514
immunology, of conventional and germfree, clearance of *E. coli* and *Staph. aureus* from blood, *1:* 504
kidney
hematocrit, *1:* 450
plasma volume, *1:* 210
weight, *1:* 90
lifespan of germfree, *4:* 95
liver
biochemistry vs. body weight, *1:* 221
blood flow, *1:* 279
cholesterol, *1:* 474; *2:* 200
fat, minerals, protein, water content, age, sex variation, *1:* 89
hematocrit, *1:* 450
inbred, of, N and P in cells, age variation, *1:* 466
nonprotein sulfhydryl compounds; effect of cold and restraint on, *1:* 120
plasma volume, *1:* 210
weight, *1:* 90, 221
lung
hematocrit, *1:* 450
plasma volume, *1:* 210
weight, *1:* 90
lymph flow, total lymphocyte output, white cell count, *1:* 405
lymphoid tissue, of conventional and germfree
histology and function; phagocytosis of particles and bacteria, *1:* 504
normal and pathologic anatomy of, *1:* 431
mammary gland of inbred, growth, *1:* 431
metabolism, basal, *1:* 66, 126, 221, 276, 371; *2:* 200
diurnal variation, *1:* 64
of obese-hyperglycemic; effect of cold on, *1:* 173
metabolism, carbohydrate
of inbred, glucose tolerance, strain variation, *1:* 191
metabolism, protein
in inbred and hairless; sulfhydryl groups in epithelium, *1:* 137
morphological and physiological characteristics of germfree, *1:* 452
muscle
hematocrit, *1:* 450
leg, weight, *1:* 90
plasma volume, *1:* 210
nervous system
audiogenic seizure susceptibility, *4:* 36
function; effect of cold on, *1:* 425
seizure patterns, *1:* 179
obesity in
blood glucose and lipids, and, *1:* 341
mechanism and reproduction, *2:* 84
physical activity; effect of drugs on, *7:* 49
physiology, genetics, *1:* 110, 135, 350
of germfree, *1:* 452
of multimammate, *1:* 350
preputial glands, weight; effect of stress on, *1:* 203
vs. population size, *1:* 204
pulse rate, *1:* 101
reproduction and sex organs, *5:* 90, 117
effect of light on field mouse, *1:* 10
estrus, and body weight, *1:* 289
effect of temperature on, *1:* 15
effect on vagina weight and glycogen content; statistical analysis, *1:* 223
induced, by gonadotropin, and number of ova in prepuberal age, *1:* 295
mating, modification by external stimuli associated with male, *4:* 67
ovulation, pregnancy, induction by gonadotrophins, strain variation, *1:* 293
suppression of, by crowding and blindness, *4:* 116
fertility
effect of population on, *1:* 348
effect of starvation on, *1:* 384
seasonal rhythm, *4:* 47
genital papilla, vascular pattern and ano-genital distance for sex determination, *1:* 313
gestation, litter number, weaning, *4:* 6
gonads; effect of olfactory bulb removal on, *2:* 125
lactation
effect of diet on, *3:* 62
in inbred, mammary gland, growth, *1:* 431
litter size
effect of diet on, *3:* 62
effect of temperature on, *1:* 330
and humidity, *1:* 36
of inbred vs. body weight, *1:* 177
litters without 2d breeding, *1:* 139
maternal age
effect of environmental temperature, humidity on, *1:* 36
inbred, at time of 1st litters, *1:* 410
litters, *4:* 26
ovary weight in young; effect of temperature on, *1:* 116
ovulation; effect of light on, *1:* 281
pregnancy, body weight
effect of estrogens on, *1:* 288
effect of temperature on, *1:* 330
eosinopenia in, and after delivery, *1:* 149
in inbred, body weight and litter size, *1:* 177
mammary gland, growth in, *1:* 431
preputial gland, effect of population on size of, *1:* 204
pseudopregnancy, body weight in, *1:* 289
reproductive cycle, time table of events, *1:* 267
seminal vesicles, size vs. population, *1:* 204
weight, effect of stress on, *1:* 203
sexual behavior in males, strain variation, *1:* 226
sexual function in young female; effect of temperature on, *1:* 116
testes, histology; effect of temperature on, *1:* 23
size, effect of population on, *1:* 204
weight, *1:* 90
effect of stress on, *1:* 203
uterus, spermatozoa and leukocytes in, and after coitus, *1:* 273
weight, in young; effect of temperature on, *1:* 116
vagina, glycogen content, *1:* 223
weight, *1:* 223
respiration, *1:* 101
constants, *7:* 164
volume, *1:* 72
reticular tissue, normal and pathologic anatomy of, *1:* 174
salivary glands, iodine uptake; effect of temperature on, *1:* 298
sex determination in newborn, *1:* 313
skeletal type of inbred, variation, *1:* 148, 181
and teeth; strain variation, *1:* 213
skin
hematocrit, *1:* 450
of inbred, sulfhydryl groups in, *1:* 137
plasma volume, *1:* 210
spine, lumbar vertebrae of inbred; x-rays, sex, strain variation, *1:* 190
spleen
age, sex variation, *1:* 89
hematocrit, *1:* 450

Mouse (*continued*)
plasma volume, *1:* 210
weight, *1:* 90
taste response, to KCl vs. NaCl, *1:* 200
teeth of inbred; strain variation, *1:* 213
thymus, weight vs. population size, *1:* 204
thyroid gland, follicle epithelial heights, of inbred; histology, age, strain variation; effect of tumor on, *1:* 377
function, of dwarf, *1:* 509
I-131 distribution in normal and tumor-bearing, *1:* 90
of inbred and hybrid, sex, strain variation, *1:* 269, 343
iodine uptake; effect of temperature on, *1:* 298
weight, *1:* 90
tissues, soft; carbon and water content, *1:* 211
use
antigen testing, mouse protection tests, *1:* 229
drug tests, *4:* 13
inbred
in acaricide tests, *2:* 318
in anesthetic toxicity tests, *6:* 48
in biochemical research, *6:* 4
in cancer chemotherapy, *4:* 65
in serological research, tissue grafting, *4:* 53
vs. genetically mixed in research, *1:* 181
insulin assay, *1:* 498
multimammate, in cancer research, in *Schistosoma* research, *1:* 350
obese, in arteriosclerosis studies, *1:* 418
pseudorabies diagnosis, *2:* 256
rabies diagnosis, *2:* 76
research, *1:* 44, 110
viral disease, *2:* 80
water consumption, *4:* 13
Mouse (strains)
fawn, *4:* 47
hairless, "naked," *1:* 137, 193, 304; *4:* 17
multimammate, *1:* 350
polydactylous, *1:* 410
Mouth examination technique, *1:* 156
Mus musculus, *1:* 348
Mus norvegicus albinus, *1:* 2
Muscular activity measurement, *7:* 117; *see also* Physical activity measurement
Mustelidae, *2:* 36, 176
Mycobacterium, *2:* 100
Mycobacterium fortuitum, *2:* 218
Mycobacterium tuberculosis, *5:* 97
Mycobacterium tuberculosis bovis, *2:* 218
Mycobacterium ulcerans, *2:* 155
Myobia musculi, *2:* 38, 48, 79, 368
Myocoptes musculinus, *2:* 38, 48, 79, 368
Myocoptes romboutsi, *2:* 79

National Cancer Institute, mouse colony, inbred and hybrids, *1:* 174
National Conference on the Legal Environment of Medical Science, *6:* 63
National Institutes of Health
animal colonies, *1:* 151; *5:* 63
tattooing methods, *6:* 54
National Institute for Medical Research, London, methods for maintenance of laboratory animals, *5:* 74
National Society of Medical Research
consultation service on animal quarters, *5:* 126
guiding principles on animal care, *6:* 63
Necropsy techniques and equipment, *1:* 101
see also Dissection
birds, *2:* 68; *7:* 100
board, for small animals, *7:* 166
cat, *1:* 18, 101, 112; *7:* 100
domestic animals, book, *2:* 68; *7:* 100
equipment procedures, carcass disposal, *2:* 68
rabbit, *1:* 81, 266; *2:* 135; *7:* 100
rat, *1:* 266
Nematospiroides dubius, *2:* 349
Neoplasms, *see* "tumors" *under* Diseases
Nervous system activity measurement, *7:* 49, 117, 188
revolving bar method in mouse, *1:* 425
righting reflex in rat, *1:* 462
New York University Medical School, animal quarters, *5:* 63
New York State Veterinary College, serological service, *2:* 195
Nipples, latex, fabrication of, *5:* 123
Nippostrongylus muris, *2:* 238, 349
Nitrofurazone, for coccidiosis prevention in rabbit, *2:* 136; *4:* 93
Nitrous oxide, *see under* Anesthesia
Nocardia sebivorans, *2:* 100
Noise, control in kennels, *5:* 44, 127
see also under Housing
effect on
inbred mouse, *1:* 179; *4:* 36
laboratory animals, *1:* 169; *5:* 108
rat, *1:* 314
exposure technique, for mouse, *1:* 179
research, use of mouse in *1:* 179; *4:* 36
Notre Dame Research Laboratories, animal colony, *5:* 18
Nursing care of small animals, *2:* 69
Nutria, book on: *Theory and Practice of Nutria Ranching*, *5:* 118
Nutrition
see also Dietary additives; Dietary supplements; Diets; "food consumption," "food requirements," "metabolism," "nutrition," "water consumption" *under* specific kind and groups of animals
books on, *3:* 15, 16, 18, 35, 37, 40, 74
Nutrition research, use of
dog in, *6:* 42
germfree animals in, *6:* 55
rat in, *1:* 510
cage for, *5:* 6

Odor
see also Housing
control and odor-free air requirements, *5:* 22
control with ultraviolet light, *5:* 58
Okatie Farms, National Poliomyelitis Foundation, monkey colony, *5:* 67
Olfactory bulb removal; effect on mouse, *2:* 125
Operation of animal colonies, *see* Administration; Breeding; Costs; Housing; Personnel; Procurement; Records; Sources of Supply; Supply department
Operations in animals and surgical equipment, *see* Surgical techniques; *see also under* Diseases
Ophthalmology, *1:* 260; *see also* "eyes" *under* specific kind and groups of animals, and *under* Diseases
Opossum
behavior patterns vs. population dynamics, *1:* 107
books and films on:
Development of Opossum, *1:* 83
Embryology of the Opossum, *1:* 30
Possums, *1:* 111
breeding, feeding, housing, *1:* 160; *4:* 8; *5:* 27, 128
development, *1:* 83
diseases, *2:* 291
embryology, *1:* 30, 111
hematology, *1:* 445
life history, *1:* 111, 160
use in pediatric research, *5:* 128
Oral
administration techniques, *see* Drenching; Feeding; Intragastric administration
examination techniques, *see* Mouth; Teeth
Organ
culture techniques, survival in synthetic medium, *7:* 192
measurement technique, *7:* 100

Pain measurement techniques, *1:* 278
in cat, *7:* 73
in dog, *7:* 20, 73
Paints for animal houses, *5:* 28, 127
Parabiosis techniques
mouse, *7:* 6
rat, *2:* 311; *7:* 6
Parakeet, *2:* 287, 321
Parasites
books, bibliographies on, *2:* 6, 55, 75, 112, 137
collection and preservation of, *2:* 112
external
see also "pest control," "sanitation" *under* Housing
control of, *2:* 44; *5:* 75
aerosols, *5:* 86
mange mites, with malathion on bedding, *2:* 368
diseases caused by, *see* "parasitic, arthropod" *under* Diseases
life cycle, transmission, *2:* 44
hosts of, *2:* 112
internal
characteristics of, *2:* 236
diseases caused by, *see* "parasitic, helminth" *under* Diseases
identification of, *2:* 66, 236
life cycle, *2:* 6, 66
tests for, *see* "parasitic" *under* Diseases, in animals; *see also* Serologic tests
transmission technique in rabbit, *7:* 35
Pasteur Institute, Dakar, *4:* 6
Pasteurella, *2:* 116
Pasteurella haemolytica, *2:* 363
Pasteurella lepiseptica, *2:* 41
Pasteurella multocida, *2:* 237, 326
"*Pasteurella pseudotularensis* n. sp.," *2:* 161
Pasteurella tularensis, *2:* 161
Pathogen-free, specific, animals
see also Disease-free animals; Germfree animals
development and maintenance of colonies, *2:* 282; *4:* 19, 72, 96, 102; *5:* 109
commercial, *4:* 68
housing for, *4:* 85
pilot, *4:* 49
program for, *4:* 37
surgical procedure for, *4:* 102
dog, *4:* 87
guinea pig, *4:* 87
helminth-free, *2:* 282
mouse, *4:* 87; *5:* 109
helminth-free, *2:* 282
Salmonella-free, *2:* 274; *5:* 121
rabbit, coccidiosis-free, *4:* 93
rat, *4:* 85, 87; *5:* 109
helminth-free, *2:* 282
internal parasite and respiratory infection-free, *4:* 49, 68
respiratory infection-free, *4:* 19, 72, 96
vs. nonspecific; differences in, *5:* 109
Pathologic techniques, *2:* 47, 72; *7:* 81
histologic, *1:* 45, 427
heart fibers, counting of, *1:* 100
stains, blood brain barrier to, in rat embryo, *7:* 104
microscopic, *2:* 47
phase microscopy, perfusion techniques, *7:* 190
preparation of tumor specimens, *2:* 25
Pathology, books on, *1:* 353; *2:* 47, 68, 72, 113, 172, 185, 207; *7:* 100
Peat moss as bedding for animals, *5:* 28
Pediatric research, use of opossum in, *5:* 128
Penicillin
see also under Dietary additives
effect on rat, *3:* 69
toxicity
for guinea pig, *2:* 119, 153
for hamster and mouse, *2:* 119
treatment of disease in cat, dog, rabbit, *3:* 17
Pentachlorophenate treatment of soil for helminth control, *2:* 362
Perfusion techniques
see also Infusion techniques
heart of rat, *7:* 54
pump for i.v. exposure in small animals, *7:* 184
Personnel in laboratory colonies, *5:* 102
see also Administration
breeding colony, *4:* 26
code for, *5:* 117
control
of epidemics in mouse colonies, *2:* 122
of infection, *2:* 124, 223
in disease-free colonies, *4:* 82
dog colonies, *4:* 100; *5:* 24; *6:* 15
duties of, *5:* 32; *8:* 4
guinea pig colony, *3:* 24; *5:* 125
health hazards to
diseases transmitted by animals, *2:* 82, 217, 323
dog bites, *8:* 15
safety measures, *8:* 3
mouse breeding program, *4:* 26, 65
mouse colony, *4:* 13; *5:* 43
organization of, *6:* 19
and responsibilities, *5:* 115
protection of, in radiation laboratories, *5:* 21; *7:* 60
against U.V. light, *5:* 101
rules, *6:* 12
relief workers; effect on animal mortality, *4:* 39
requirements, for dog colonies, *4:* 100
and duties, *8:* 2
responsibilities of, *8:* 4, 14; *5:* 115
for laboratory animal colonies, *5:* 123
standards, California, *6:* 33
for dog care, *6:* 15
time required
for cage cleaning, *5:* 30
for care, and maintenance of mouse colony, *4:* 13
of monkey, *5:* 134
of rat, *5:* 21
for growing and feeding bean sprouts to guinea pig, *3:* 24
for hamster breeding and raising, *4:* 10
for tube feeding rats, *3:* 6
time requirements, costs, *4:* 83
training, *5:* 89
Gt. Britain, *5:* 74; *8:* 4, 11, 13
inbred mice breeding colonies, *4:* 65
Mexico, *5:* 90
sanitation, *5:* 84
specific pathogen-free colony, *4:* 49; *5:* 109, 129
veterinary consultation, for control of infection in cats and dogs, *2:* 124
Pest control, *see under* Housing
Pesticides
see also Lindane; Malathion; Piperonyl butoxide; "chemical agents" *and* "parasitic, arthropod" (control, treatment) *under Diseases*
cause of disease in guinea pig, *2:* 186
control of parasites, *2:* 24, 48, 105, 268
DDT for eradication of *Leptospira ballum*, *2:* 280
safety for laboratory animals, *2:* 45
Pharmacologic research
see also "chemical agents and drugs" *under* Diseases
toxicity tests; effect of environmental temperature on, *1:* 59; *2:* 10; *6:* 37
use of
animals in, *see also under* specific tests, and *under* specific kind of animal
cat in choleretic agents tests, *6:* 18
guinea pig in antiallergen tests, *7:* 32

Pharmacology, books on, *2:* 172, 279; *7:* 164; *see also* Drugs
Phenothiazines
control of diseases, *2:* 31, 190
effect on water intake of rat, *7:* 185
Philadelphia Zoological Gardens, disease control in, *2:* 70, 341
Phlebothrombosis research, use of hamster in, *2:* 108
Phthalates in control of parasitic diseases, *2:* 87
Photography
mouse, salamander, *7:* 46
time-lapse, tissue culture chamber for, *7:* 190
wild rat, *5:* 106
Physical activity measurement
see also "physical activity" *under* specific kind of animal
cat; ergometer, *7:* 163
dog; treadmill, *1:* 516
monkey
device for, *7:* 188
jumping, device for, *7:* 177
mouse, *7:* 49, 97
rat
stabilimeter, wheel cages, *1:* 157, 175
swimming speed, device for, *1:* 331
small animals, *1:* 429; *7:* 75, 97, 136
running, device for, *7:* 68
Physical examination, of dog, *2:* 330; *see also* special techniques
Physiology, books on, *see under* Books etc.; for physiology of animals, *see under* specific kind and groups of animals
Pig
see also Swine
miniature, genetics, *4:* 44, 74
use in research, *4:* 35, 44, 61, 74
Pigeon
see also Birds; Breeding; Diets; Diseases
anatomy, *1:* 311
blood
cholesterol, *1:* 474
hematology, *1:* 71, 403
lipids (in Carneau), *6:* 53
serum, bile, liver, cholesterol, *1:* 474
bone marrow, cytology, *1:* 403
books on: *The Pigeon*, *1:* 311
eye
physiology, *1:* 311
retinal circulation, *1:* 192
use in atherosclerosis research, *2:* 306; *6:* 53
Pinnepedia, body, organ, gland weights, *1:* 37
Piperazine
in control of diseases, *2:* 190, 327
toxicity for cat, dog, mouse, *2:* 129
Piperonyl butoxide, toxicity for laboratory animals, *2:* 45
Plasma volume determination with radio-I, *1:* 210
Plasmodium, *2:* 14
Plasmodium berghei, *2:* 143
Plasmodium lophurae, *2:* 57
Plethysmometric technique, *7:* 95
Pneumoderma pouch technique, in rat, *7:* 115
Pneumogram, recording in rabbit, *7:* 88
Pneumonyssus foxi, *2:* 158
Poisoning of animals, *see* "chemical agents and drugs" *under* Diseases
Polyplax serrata, *2:* 79
Population dynamics
caging, double or single, effect on rat, *1:* 258
crowding
effect on
hamster, *1:* 361; *3:* 50; *4:* 60
laboratory animals, *1:* 169
mouse, *4:* 116
rat, *1:* 361
grouping, effect on mouse, *2:* 214
isolation
effect on dog, *1:* 264
effect on mouse, *1:* 253, 416; *2:* 214
population density
effect on mouse, *1:* 203, 204, 498; *2:* 305
effect on "wild house" mouse, *1:* 348
social aspects of
in animals, and behavior, *1:* 107
territorial organization in wild, captivity; effect on rat, *1:* 417
Posological tables for small animals, *2:* 69
Poultry
see also Birds; Breeding; Chicken; Diets; Diseases; Domestic animals; Handling; Housing
anatomy, *2:* 298
behavior patterns, *2:* 298
books on: *Diseases of Poultry*, *2:* 298; *see also under* Domestic animals
digestion, *2:* 298
genetics, *5:* 49
and pathology, *2:* 298
hematology, *2:* 298
nutrition, nutritive requirements, *2:* 298
reproduction, *5:* 90
Pregnancy, physiologic effects of, *see* "reproduction and sex organs" *under* specific kind and groups of animals
Pregnancy determination
in laboratory animals, *2:* 47; *7:* 81
in rabbit; standard operating procedure, *5:* 123
use of frog in, *5:* 56
Pressure chamber, for rabbit, cat, guinea pig, *7:* 144
Primates, subhuman, *see* Monkey
Procurement of
see also Administration; Sources of supply
animals
costs of breeding vs. buying, in Gt. Britain, *6:* 26
for disease-free colonies, *4:* 82
inbred, infection-free animals, in Great Britain, *6:* 26
purchasing policy manual, *6:* 51
receiving, and, *5:* 21
rules, *6:* 12
specifications, book, *5:* 123
cat, from pounds and owners, *6:* 13
dog, *5:* 24
from pounds and owners, *6:* 13, 20
guinea pig, *5:* 40
mouse, inbred; contracts, specifications, *4:* 65
poultry, *5:* 49
primates, in Gt. Britain, *6:* 26
rabbit, domestic, and selection of breed, *4:* 58
rat, *1:* 87
Procyonidae, *2:* 36
Production of animals, *see* Breeding
Protozoa
for diseases caused by *see* "protozoan" *under* Diseases; *see also* Parasites; Serologic tests
life cycle of, *2:* 66
tests for, in rat blood, *2:* 143
Pseudomonas pyocyanea, *2:* 100
Pseudorabies (Aujeszky's disease) diagnosis, use of animals in, *2:* 256
Psorergates simplex, *2:* 79, 87, 318
Psychologic research, use of rats in, *1:* 87, 417
Psychology of animals, *see* "behavior patterns" *under* specific kind of animal
Public relations, and use of dog in research, *5:* 24
Purchasing, *see* Procurement
Pyelography, *see under* Radiology
Pyrexia, *see* "fever" *under* Diseases
Pyrimethamine, in treatment of disease, *2:* 78, 159, 203
Pyrogens, sensitivity of guinea pig, rabbit to, *6:* 34

Quarantine (isolation)
see also "isolation" *under* Cages; for effects, see Population dynamics
cat, *2:* 124, 317
incoming, *2:* 74
dog, *2:* 124
guinea pig, *5:* 125
laboratory animals, *1:* 135; *2:* 32; *5:* 18, 21, 74, 123
monkey, *2:* 32; *5:* 96; (chimpanzee) *5:* 61
new arrival, *2:* 30, 70
rabbit, domestic, *4:* 58
rat in disease control, *4:* 19
report on, *6:* 39
rooms, design of, *5:* 17
Queensland Institute of Medical Research, *2:* 264

Rabbit
see also Anesthesia; Animals; Breeding; Diets; Diseases; Domestic Animals; Handling; Housing; Laboratory Animals; Mammals; Restraint; Vertebrates
adrenal glands; adrenocortical secretion; species variation, *1:* 125
anatomy, comparative; histology, *1:* 489
weight, *1:* 134
effect of sperm removal on; pathology, *4:* 88
effect of temperature on; histology, *1:* 456
anatomy, *1:* 81, 135, 254; *2:* 9
dissection, and, *1:* 266
domestic, *2:* 135
functional, *1:* 62
gross and microscopic, *1:* 94
behavior patterns
maternal, *1:* 352
vs. population dynamics, *1:* 107
wild, *1:* 263
bile, cholesterol, *1:* 474
blood
anemia in pregnancy, *1:* 303
cellular elements, *2:* 47; *see also* "erythrocytes," etc.
cholesterol, serum, *1:* 474, 502; *see also* "lipids"
coagulation, *1:* 12, 71, 403, 445; *7:* 19
effect of injury on, *7:* 19
prothromboplastin activities, *1:* 291
electrolytes, *1:* 109, 403, 502
erythrocytes, *1:* 8, 71, 91, 101, 403, 445
age variation, *1:* 11, 12
from central or peripheral vessels, *1:* 82
lifespan, *1:* 50
number, size, hemoglobin content, corpuscular volume; sex variation, *1:* 24
hematocrit, *1:* 71, 445
age variation, *1:* 11
hemoglobin, *1:* 8, 71, 91, 101
age variation, *1:* 11, 12
hemolysis, *1:* 12
hormones, thyrotropic and gonadotropic, in mature and immature, *1:* 261
leukocytes, *1:* 8, 12, 71, 91, 101, 403, 445
lipids, *1:* 403
see also "cholesterol"
in gray Chinchilla, *1:* 412
lymphocytes, lifespan, *1:* 249; *see also* "leukocytes"
picture; variation with age, sex, pregnancy, diet, anesthesia, species, *1:* 12
plasma volume, *1:* 49
platelets, *1:* 101
proteins, serum, *1:* 270, 403, 502
amino acids, *1:* 134
electrophoretic analysis for selection of normal animals, *1:* 323
glycoproteins of New Zealand; sex variation, effect of blood loss on, *1:* 242
of gray Chinchilla, *1:* 412
reticulocytes, *1:* 71
see also "erythrocytes"
age variation, *1:* 11
reticuloendothelial system, phagocytic response of, *1:* 279
sedimentation rate, *1:* 71, 403, 445
specific gravity, *1:* 12, 71
sugar, *1:* 403, 412
urea concentration, *1:* 68
viscosity, *1:* 403
volume, *1:* 12, 49, 71
water, plasma, *1:* 109
blood pressure, ear veins and arteries, *1:* 441
blood types, *1:* 232, 467
genetics, *1:* 346
nomenclature, *1:* 205
blood vessels, cholesterol biosynthesis *in vitro*, *1:* 326
body, chemical composition; age, sex variation, *1:* 89
body fat, *1:* 89, 142
body heat production, *5:* 22
effect of environmental temperature on, *1:* 306
body length of normal and dwarf, *1:* 310
body temperature, *1:* 101
domestic, *1:* 292
effect of environmental temperature on, *1:* 306, 379
body water, *1:* 89, 172
loss, respiratory and surface of New Zealand vs. temperature, *1:* 379
body weight, *1:* 134
see also "growth"
at birth; genetic effects, *1:* 227
gain; effect of weaning on, *4:* 107
vs. environmental temperature, *1:* 379
vs. liver biochemistry, *1:* 221
bone marrow
chemistry, *1:* 63
cytology, *1:* 403
books, bibliographies, periodicals on
American Rabbit Journal, *9:* 1
Anatomy, *1:* 62, 81, 94
Dissection of Rabbit, *1:* 266
Domestic Rabbit Production, *4:* 58
4-H Rabbit Raising Handbook, *5:* 110
Rabbit, *1:* 263
Rabbit and Cat Diseases, *2:* 1
Rabbit as Used in Disease Research; Selected Bibliography, *2:* 9
Rabbits' Ailments, *2:* 135
Rabbits, a Subject Bibliography, *1:* 254
Raising Rabbits, *4:* 155
Reproduction in the Rabbit, *1:* 4
brain, water content, age variation, *1:* 212
constitutional strength as measured by resistance to thirst; breed variation in domestic, *1:* 118
coprophagy in, *1:* 494
digestive tract
fluid volume, *1:* 172
intestinal lymphoid tissue, bacterial infiltration in; effect of aureomycin, *2:* 92; *see also* "feces"
length and weight of normal and dwarf male and female, *1:* 310
embryology, *1:* 83
enzymes
amylase, serum, *1:* 412
cholinesterase in heart, *1:* 168
transaminases, oxidases, total body activity; body weight and sex variation, *1:* 476
eyes
anatomy and physiology, *1:* 260
retinal circulation, *1:* 192
feces, fecal flora, *1:* 246

Rabbit (*continued*)
moisture vs. temperature, of New Zealand, *1:* 379
vitamin B_{12} in, *1:* 494
fetus
brain, water content, *1:* 212
fluid content, *1:* 267
food consumption, *3:* 34, 53; *5:* 117
see also "nutrition"
birth, from, of Chinchilla-giganta, *3:* 47
effect of environmental temperature, *1:* 306, 379
food requirements, *3:* 13
see also "nutrition"
standard values, *3:* 35
vitamins, *3:* 53
effect on reproduction, *3:* 5
weaned New Zealand; effect of season, castration, age, disease on, *3:* 15
genetics and blood types, *1:* 205, 346
and maternal behavior, *1:* 352
growth, and development
see also "body weight, length"
effect of heat on, *1:* 307
effect of P diet on, *3:* 52
hair growth, in albino and colored, *1:* 57
reaction to injury, *1:* 366
replacement, type, *1:* 99
heart, EKG; effect of vitamin E-deficient diet on, *1:* 97
weight, *1:* 134
immune bodies
antibodies in blood, complement, titer, *1:* 229
after protein challenge; age variation, *1:* 446
against parotitis, psittacosis, toxoplasmosis, *1:* 391
and protein turnover, *1:* 505
antigens
in blood, *1:* 232, 467
in spermatozoa and seminal plasma of Dutch Belted, *1:* 413
transmission from mother to young, *1:* 369
kidney function
albumin in urine and total albumin loss, *1:* 502
urea in blood and urine, *1:* 68
weight, *1:* 134
lactation, milk yield in Chinchilla-giganta and suckling period, *3:* 47; *see also* "reproduction"
liver
see also "metabolism, carbohydrate"
biochemistry; age, sex variation, *1:* 89
biochemistry vs. body weight, *1:* 221
blood flow, *1:* 279
cholesterol, *1:* 474
weight, *1:* 134, 221
lung, pressure, volume, *1:* 167; *see also* "metabolism, carbohydrate," "respiration"
lymphatic system, output of lymphocytes, *1:* 249
metabolism, basal, *1:* 221
vs. environmental temperature, of New Zealand, *1:* 379
metabolism, carbohydrate; glycogen content in muscle, liver, lungs of newborn and adult, *1:* 239; *see also* "blood, sugar"
sugar tolerance, *1:* 152
metabolism, mineral, *1:* 89
effect of low P diet, *3:* 52
iron, effect of pregnancy on, *1:* 336
metabolism, protein, *1:* 89, 270
see also "blood, proteins"
amino acid content of serum, liver, kidney, muscle, thymus, *1:* 134
muscle, electrolytes and water, *1:* 109; *see also* "metabolism, carbohydrate"
nutrition, *2:* 9
see also "food consumption," "food requirements"
of domestic, *2:* 135
physiology, *1:* 135, 254; *2:* 9
of domestic, *2:* 135
of wild, *1:* 263
pulse rate, *1:* 101
vs. environmental temperature, of New Zealand, *1:* 379
reproduction and sex organs, *1:* 4, 353, 438; *2:* 9; *5:* 90, 117
see also under Breeding
effect of diet on, *3:* 5, 52
estrus and hormones in blood of mature and immature, *1:* 261
fertilization, spermatozoa transport, *1:* 395
fetal fluid, placental type, endometrial differentiation, *1:* 267
fetal resorption; effect of temperature on, *1:* 312
insemination with mixed semen; effect on weight of offspring, *1:* 227
maternal behavior, *1:* 352
pregnancy
anemia in; endocrine aspects, *1:* 303
determination of, *5:* 123
iron metabolism and placental transport in, *1:* 336
sugar tolerance in; effect of cortisone on, *1:* 152
pseudopregnancy and hormones in blood, *1:* 261
semen
antigen production in, *1:* 413
counts; age, individual variation, *1:* 236
motility and fertilizing capacity of wild, effect of urine on, *1:* 345
removal; effect on weight; pathology, *4:* 88
transport in female, *1:* 243
uterus, bactericidal activity of estrous, spayed, pseudopregnant, *2:* 61
wild, *1:* 263
respiration, *1:* 101
see also "lung"
anatomy, mechanics, physiology, *1:* 394
constants, *7:* 164
in newborn; reflex mechanism, *1:* 443
rate vs. environmental temperature, of New Zealand, *1:* 379
volume, *1:* 72
spleen, bacterial infiltration in, effect of aureomycin on, *2:* 92
biochemistry; age, sex variation, *1:* 89
weight, *1:* 134
taste response, to KCl vs. NaCl, etc., *1:* 200
thymus, bacterial infiltration in, effect of aureomycin on, *2:* 92
weight, *1:* 134
thyroid gland function, effect of heat on; age variation, *1:* 307
effect of temperature on, *1:* 306, 379
urine
effect on spermatozoa, *1:* 345
moisture loss vs. temperature, *1:* 379
urea concentration, *1:* 68
volume and specific gravity, *1:* 502
use for
disease research, *2:* 9
iso-immunization studies, *1:* 232
pseudorabies diagnosis, *2:* 256
rabies diagnosis, *2:* 76
vitamin B_{12} metabolism, *1:* 494
water consumption of New Zealand vs. environmental temperature, *1:* 379
Rabbit and Cavy Breeders' Industry, trade practice rules, *6:* 50
Raccoon
body temperature, *1:* 292
hematology, *1:* 445
taste response, to KCl vs. NaCl, *1:* 200
Radfordia affinis, *2:* 79
Radiation
see also "physical agents" *under* Diseases
effects of
cells, *1:* 427
circulation, *1:* 486
emetic apparatus of cat, *1:* 430
fate in organism of animals, and, *7:* 56

Radiobiologic research
  see also Radioisotope techniques
  cage-hood assembly, *5:* 47
  cages
    for mouse, *5:* 54
    for rat, *5:* 54, 124
    restriction, for mouse, *5:* 33
  carcass preservation and disposal, *5:* 95
  decontamination, *5:* 130
  drug administration to rat, *3:* 38
  exposure chamber for, *7:* 43, 176
    mouse, *7:* 147
  handling of animals, in, *5:* 79
    before and after isotope administration, *5:* 79
  housing and care of animals, *4:* 100; *5:* 39, 61, 79, 115; *6:* 22
  metabolism cage for miniature pigs, *5:* 130
  production and maintenance of dog for, *4:* 100
  protective measures for personnel, *7:* 60
  specifications for animal laboratories, *5:* 21
  use of animals in, *3:* 38; *6:* 56
    selection, *6:* 22
Radioisotope techniques, *6:* 22, 56; *7:* 164
  see also under Blood study techniques; Radiobiologic research
  administration of isotopes
    to cattle, sheep, swine, *7:* 31
    to guinea pig, mouse, rat, and balance studies in, *7:* 55
  clearance of isotopes from dog, rabbit, rat, *7:* 56
  glucose metabolism with C-14 in rat, *1:* 217
  Harderian gland function with radio-iodine, in mouse, *1:* 298
  iodine distribution in mice with and without tumor, *1:* 90
  liver blood flow with radio-iodine, in animals, *1:* 279
  metabolism in
    animals, *7:* 140
    cattle, *7:* 31
    dog, *5:* 55
    guinea pig, *1:* 302
    sheep, swine, *7:* 31
  reticuloendothelial system, phagocytic response of, *1:* 279
  salivary gland function with radioiodine, in mouse, *1:* 298
  thyroid gland function, *2:* 307
    with radio-iodine
      in guinea pig, *1:* 302
      in mouse, *1:* 298
      in rat, *1:* 349
  urea hydrolysis, in rat, *1:* 475
  vitamin B_{12} absorption in rabbit, *1:* 494
  waste disposal, *7:* 60
Radiology
  animals, *2:* 54, 353
  chest of monkey, restraint table for, *7:* 120
  cholecystography in cat, dog, *2:* 95
  ear of rat, *2:* 101
  effect on tumor incidence in rat, *2:* 339
  kidney of dog, *7:* 101
  myelography of dog, *7:* 85
  rat, *1:* 45
  skeleton, of mice, *1:* 190
  skull
    of cat, *1:* 459
    of dog, *2:* 239
  spine, of dog, *2:* 329
  spleen, arterial patterns in normal and tumor-bearing rat, *1:* 338
  urinary tract, of retrograde and i.v. pyelograms of cat, dog; dosage scale of contrast medium, *7:* 44
  ventriculography in rabbit, *2:* 179
Rana pipiens, *see* Frog
Rat
  see also Anesthesia; Animals; Breeding; Diets; Diseases; Handling; Housing; Mammals; Restraint; Rodents; Vertebrates
  adrenal glands
    adrenocortical secretion, species variation, *1:* 125
    anatomy, comparative; histology, *1:* 489
    ascorbic acid and cholesterol content at room and low temperatures; effect of restraint on, *1:* 224
    effect on hair growth, *1:* 378
    weight
      effect of antibiotic on; pathology, *2:* 275
      effect of gentling on, *1:* 197
      gray Norway; effect of captivity on, species variation, *1:* 7
      histology, of normal, pregnant and pseudopregnant, and fetus, *1:* 284
      inbred; effect of diet on; histology, *1:* 492
  anatomy, *1:* 2, 45, 135, 453
    compared with multimammate mouse, *1:* 350
    dissection, *1:* 266
  behavior patterns, *1:* 87
    see also "learning"
    anxiety, maternal, and in offspring, *1:* 320
    effect of
      drugs on, *7:* 155
      extra handling on, *1:* 194
      gentling on, *1:* 197
      shock on, *1:* 411
      tranquilizers on, *7:* 143
    fighting, induction of, *7:* 191
    mating response, *4:* 30
    social and territorial organization of colonies in wild and captivity, *1:* 417
    vs. population dynamics, *1:* 107
    wild gray Norway; effect of captivity on, *1:* 35
  bile, cholesterol, *1:* 474
  biology of brown, *5:* 106
  blood
    cholesterol
      plasma, *1:* 458
      serum, *1:* 474
    coagulation, *1:* 12, 71, 403
      effect of tropical heat on, *2:* 13
      prothrombin time; effect of stress on, *1:* 314
      prothromboplastin activities, *1:* 291
    electrolytes, *1:* 403
      Ca, strain variation, *1:* 271
        K, serum; effect of heat, restraint on, *1:* 449
      Cl, K, Na, *1:* 109, 464
      K, in inbred, strain variation, *1:* 271
      Na, strain variation, *1:* 271
        K content of plasma of normal, pregnant, pseudopregnant
          and fetus, *1:* 284
          in inbred, *1:* 364
      P; effect of diet and temperature on, *1:* 195
    eosinophil rhythm, diurnal variation, in inbred, *1:* 183
    eosinophils, age, disease variation, *1:* 359
    erythrocytes, *1:* 12, 53, 71, 79, 101, 359, 403
      central or peripheral vessels, *1:* 82
      effect of
        diet and heat on, *1:* 138
        lactation on, *1:* 334
        protein deficiency on, *2:* 201
      number, size, hemoglobin content, corpuscular volume, sex variation, *1:* 24
      volume, and age variation, *1:* 294, 488
    fatty acid peroxides, *1:* 471
    hematology, *1:* 45
      see also specific constituents
      age, sex, pregnancy, diet, anesthesia, species variation, *1:* 12
    hematocrit, *1:* 55, 71
      age variation; effect of castration on, *2:* 233
      effect of
        cold on, *1:* 458
        diet on, *1:* 510

Rat (*continued*)
heat, restraint on, *1:* 449
lactation on, *1:* 334
hemoglobin, *1:* 24, 71, 101
age variation, *1:* 12, 53, 294, 359
effect of
cold on, *1:* 458
diet on, *1:* 510
disease on, *1:* 359
lactation on, *1:* 334
hemolysis, *1:* 12
ketones, *1:* 458
leukocytes, *1:* 55, 71, 93, 98, 101, 403
age, disease variation, *1:* 12, 359
effect of heat and diet on, *1:* 138
heart and peripheral, *1:* 78, 79
lipids, *1:* 403
see also "cholesterol"
phospholipids, *1:* 458
lymphocytes, renewal in thymus, *1:* 402; *see also* "leukocytes"
nitrogen, residual, serum, *1:* 93
effect of cold on, *1:* 458
oxygen capacity, age, sex variation, *1:* 282
packed cell volume, *see* "erythrocytes," "volume"
plasma volume, *1:* 294, 334, 347
platelets, *1:* 101
proteins,
plasma, circulating
age variation, *1:* 53
effect of cold on, *1:* 458
effect of lactation on, *1:* 334
serum, *1:* 512
γ-globulin
in conventional and germfree, *1:* 514
in germfree, *1:* 370
lability to diets, *1:* 510
total and globulin, in black, *1:* 93
pyruvate levels, *2:* 143
reticulocytes, of black, *1:* 71, 93
reticuloendothelial system, phagocytic activity, *1:* 279
sedimentation rate, *1:* 71, 403
specific gravity, *1:* 12, 71
effect of heat, restraint on, *1:* 449
of plasma; effect of cold on, *1:* 458
sugar, *1:* 403
glucose; effect of cold on, *1:* 458
viscosity, *1:* 403
vitamin B_{12} in serum; effect of diet, *1:* 406
vitamins; effect of diet and temperature on, *1:* 195
volume, *1:* 12, 71; see also "erythrocytes," "plasma"
cellular, *1:* 347
effect of lactation on, *1:* 334
extracellular, *1:* 364
partition, age variation, *1:* 53
water, plasma, *1:* 109
effect of acute fasting on, *1:* 464
effect of cold on, *1:* 458
weight, *1:* 230
blood pressure, *1:* 225
age, sex, species variation, *1:* 58; *2:* 370
arterial, *1:* 130
of inbred, *1:* 364
of normal and hypertensive, *1:* 268
systolic, *1:* 145
blood vessels
arterial patterns of spleen, radiographs, *1:* 338
capillaries, morphological classification, *1:* 423
cholesterol biosynthesis in vitro, *1:* 326
in ears, heart, liver, muscles; effect of acclimation to cold on, *1:* 300
body composition, age variation, *1:* 233
body electrolytes; effect of fasting on, *1:* 464
body fat, *1:* 372
age variation, *1:* 233
to body water relationship, *1:* 199
density, *1:* 142
effect of acute fasting on, *1:* 464
fatty acid peroxides in tissue, *1:* 471
of normal, starved, and dehydrated, *1:* 164
weight, *1:* 230
body heat production, *1:* 126; *5:* 22; *see also* "metabolism, basal"
body length
effect of gentling on, *1:* 258
vs. body weight of gray Norway; effect of captivity on, species variation, *1:* 7
body measurements, *5:* 21
body size, and susceptibility to pantothenate deficiency disease, *2:* 192
body temperature, *1:* 101
core to surface gradients, at various environmental temperatures; effect of restraint and hair removal on, *1:* 327
diurnal variation, *1:* 183
effect
of cortisone on, in cold and under restraint, *1:* 224
of heat, restraint on, *1:* 449
of restraint on, mechanism, *1:* 328
rectal; effect of gentling on, *1:* 197
body tissues
connective, protein, collagen composition, age, sex variation *1:* 469
mitoses in inbred, diurnal variation, *1:* 183
soft, carbon and water content, *1:* 211
weight, *1:* 230
body water
age, sex variation, *1:* 89
balance, *1:* 172, 188
effect of diet on, *1:* 493
economy after protein and urea feeding and dehydration, *1:* 373
effect of acute fasting on, *1:* 464
fat-free body relationship, *1:* 199
normal, starved, and dehydrated, *1:* 164
soft tissues, *1:* 211
total, intra- and extracellular, age variation, *1:* 233
body weight
age variation, *1:* 233
daily, of mature, on constant diet, *1:* 52
effect of
acute fasting on, *1:* 464
altitude and temperature on, *1:* 385
altitude on thermally conditioned, *1:* 387
captivity on, species variation, *1:* 7
cold on, *1:* 426
diet and antibiotics on, *2:* 244
gentling on, *1:* 197, 258
hypervitaminosis on, *2:* 354
litter size on, *1:* 334
single-food-choice diet on, *3:* 19
temperature on, *1:* 386
gain, *1:* 372
effect of
diet on, *3:* 70
handling on, mechanism, *7:* 121
normal, starved, and dehydrated, *1:* 164
ratio of organ weight to, *1:* 76
suckling, and "milking" glands of mother, *1:* 235
vs. bone growth and age, *1:* 69
wild gray Norway; effect of captivity on, *1:* 35
bone marrow
cell count, differential, and cell distribution, age variation, *1:* 432
cell count, in femoral, *1:* 75
cytology, *1:* 403
myelogram, age variation, *1:* 55

Rat (*continued*)
bones, growth of, age and body weight variation, *1:* 69
books on
Anatomy, *1:* 453
Anatomical and Physiological Studies on the Growth of the Inner Ear of the Albino Rat, *1:* 1
Breeding and Care of Albino Rat for Research Purposes, *4:* 2
Care of Small Rat Colony, *5:* 12
Dissection of the Rabbit, with Appendix on the Rat, *1:* 266
Genesis of the Rat Skeleton, *1:* 321
Life Processes in Gray Norway Rats During 14 Years in Captivity, *1:* 35
Life Processes and Size of Body and Organs of Gray Norway Rat During 10 Generations in Captivity, *1:* 7
Psychological Research on Rat, *1:* 87
Rat: Data and Reference Tables for the Albino and Norway Rat, *1:* 2
Rat in Laboratory Investigations, *1:* 45
Rat Quality, *1:* 151
Skeletal Development of the Rat, *1:* 121
brain
calcium content, age variation, *1:* 409
weight, *1:* 230
age variation, *1:* 233
and cholinesterase activity, individual variation, *1:* 329
effect of captivity on, species variation, *1:* 7
effect of temperature on, histology, *1:* 456
cannibalism, filicidal in; effect of diet on, *4:* 90
cardiovascular system,
see also "blood pressure," "blood vessels," "heart," "pulse rate"
pathology; effect of gentling on, *1:* 197
defecation, emotional, measurement of, *1:* 158
development, *see under* "body," "growth"
digestive tract
see also "feces," "gastric juice," "intestines," "stomach"
effect of gentling on, *1:* 197
fluid volume, *1:* 172
nitrogen content, *1:* 365
weight of contents, *1:* 230
ear, inner, growth of, anatomy and physiology, *1:* 1
endocrinological reactions in inbred, variability in littermates, *4:* 52; *see also* "adrenal glands," etc.
enzymes
cholinesterase, in blood, *1:* 219
cholinesterase, in brain, age, strain, individual variation, *1:* 329
malic and succinic dehydrogenase in heart, kidney, liver brain, body size variation, *1:* 143
phosphatase, alkaline, in serum; effect of diet and temperature on, *1:* 195
effect of Mn deficiency on, age variation, *1:* 463
succinic dehydrogenase in liver; effect of altitude and temperature on, *1:* 389
transaminases, oxidases, total body activity; body weight, sex variation, *1:* 476
urease of intestinal bacteria, *1:* 475
eyes, retinal circulation, *1:* 192
feces, fecal flora, *1:* 246
see also "digestive tract"
residues, dimensions of; effect of diet on, *1:* 483
volume, age variation, *3:* 67
fetus, adrenal glands, weight, *1:* 284
see also "reproduction and sex organs"
blood plasma, electrolyte (Na, K) content, *1:* 284
body weight vs. mother's weight, *1:* 284
glycogen content of liver, *1:* 339
muscle, electrolyte (Na, K) content, *1:* 284
water content, *1:* 284
pituitary gland, weight, *1:* 284
food absorption, and nitrogen content of gastrointestinal contents, *1:* 365
food consumption, *3:* 34
age variation, *3:* 67
effect of
altitude and temperature on, *1:* 385
growing, *3:* 14
hypervitaminosis on, *2:* 354
liver in lactating, *1:* 381
manipulation of motivation on growth, *3:* 82
temperature on, *1:* 195, 312; *3:* 10
osmotic capacity of dietary carbohydrates, *3:* 70
seasonal variation, *3:* 12
utilization; effect of antibiotics on, *3:* 69
vs. body weight, mortality, behavior, *2:* 51
vs. longevity and old-age diseases, *2:* 18
food requirements, *1:* 45; *3:* 8, 13, 46
caloric, *3:* 56
for growing, *3:* 14
standard values, *3:* 35
vitamins; effect of temperature on, *3:* 10
zinc, *2:* 252
food utilization
effect of extra handling on; mechanism, *1:* 194
effect of gentling on, *1:* 258
gastric juice, volume and acidity, *1:* 117
genetics, *1:* 2, 151
inbred and random bred, *4:* 109
mutations in wild gray Norway; effect of captivity on, *1:* 35
variability in inbred; reduction by crossed lines, *4:* 52
vs. body weight and growth, *4:* 29
growth, *1:* 2
see also "body length, measurement, size, weight"
criteria, *1:* 151
development of Merriam's kangaroo, *1:* 436
development, early, *1:* 73
effect of
diet on, *3:* 14, 62
diet and temperature on, *1:* 195
drugs on, *3:* 41
extra handling on, *1:* 194
food consumption on, *3:* 82
food consumption and seasons on, *3:* 12
temperature on, *3:* 10
skeletal, atlas of normal and hypophysectomized, *1:* 121
wild gray Norway; effect of captivity on, *1:* 35
young; effect of light on, *1:* 132
hair, color of black, black hooded, gray coated; effect of nutritional anemia on, *2:* 3
growth, *1:* 366
replacement, type, *1:* 99
sex variation; effect of sex hormones, adrenalectomy, spaying and castration on, *1:* 378
heart, action and weight during exercise, *1:* 100
cellular metabolism, age variation, *1:* 277
EKG, age variation, *1:* 358
glycogen content in pregnancy, *1:* 339
rate, *1:* 70
age variation, *1:* 147
weight, *1:* 230
age variation, *1:* 233, 358
effect of temperature on, *1:* 456
immune bodies
antibodies in blood, *1:* 93
complement, titer, *1:* 229
heterohemagglutinins, antibacterial agglutinins, properdin, complement titers in blood of conventional and germfree, *1:* 508
immunity, in conventional and germfree, *1:* 514
intestines, capacity, dimensions; effect of diet on, *1:* 483
see also "digestive tract"
cecum distention development, in conventional and germfree, strain variations, *1:* 515
growth; effect of diet on, *1:* 483

Rat (*continued*)
morphology of lymphoid tissue of conventional and germfree, *1:* 503
weight, *1:* 230
and length; effect of diet and antibiotics, *2:* 244
kidney
anatomy, histologic changes with age, *2:* 126
cellular metabolism, age variation, *1:* 277
function
see also under "metabolism, mineral; protein"
creatinine, Na, K, clearances; effect of drugs on, *1:* 251
nitrogen, electrolyte excretion; effect of altitude, temperature on, *1:* 388
protein, NPN, creatinine, uric acid excretion in urine, age variation, *1:* 357
solute concentration after urea and protein feeding, *1:* 373
weight, *1:* 76, 230
age variation, *1:* 233
effect of temperature on; histology, *1:* 456
lactation, *see under* "reproduction and sex organs"
learning ability; effect of adrenalectomy, handling on, *7:* 121
lifespan, *2:* 90
effect of
food intake on, *2:* 18
radiation and high temperature on, *2:* 302
liver
biochemistry vs. body weight, *1:* 221
blood flow, *1:* 279
cellular metabolism, age variation, *1:* 277
cholesterol, *1:* 474
fat, mineral, protein, water in, age, sex variation, *1:* 89
glycogen content of fetal and maternal in pregnancy, *1:* 339
growth and protein, deoxyribonucleic acid content; effect of lactation, food intake on, *1:* 381
pathology in aged, *2:* 232
weight, *1:* 76, 221, 230
age variation, *1:* 233
effect of temperature; histology, *1:* 456
longevity, *see* "lifespan"
lung, weight, *1:* 230
lymph nodes, morphology of conventional and germfree, *1:* 503
mammary gland, growth in pregnancy and lactation, *1:* 454
metabolism, basal, *1:* 126, 221, 371, 429
age variation, *1:* 233
effect of
drugs on, *1:* 161
hypervitaminosis on, *2:* 354
physical activity on, *1:* 217
temperature on, *1:* 312
oxygen consumption, age variation, *1:* 147
effect of cold and restraint on, *1:* 419
metabolism, carbohydrate
effect of physical activity on, *1:* 217
of mother and fetus in pregnancy, *1:* 339; *see also* "blood, pyruvate; sugar"
metabolism, fat, *1:* 471
see also "blood, cholesterol; lipids," "body fat"
age, sex variation, *1:* 89
body cholesterol, fatty acids; effect of altitude and temperature on, *1:* 389
metabolism, mineral
see also "blood electrolytes," "body electrolytes"
age, sex variation, *1:* 89
calcium in brain, age variation, *1:* 409
Ca, K, Mg, Na, PO_4 excretion; effect of altitude, temperature on, *1:* 385, 387, 388
effect of temperature on, *1:* 386
Ca utilization, in growing, promotion of bone formation by lactose, *3:* 48
metabolism, protein
see also "blood, proteins," "kidney function"
age, sex variation, *1:* 89, 469
N balance, dietary variation, *1:* 265
protein content, body, *1:* 372, 469
S balance in rat, dietary variation, *1:* 414
urea hydrolysis and mechanism, *1:* 127
of conventional and germfree, *1:* 475
urea, uric acid, amino acid excretion; effect of altitude and temperature on, *1:* 385, 387
uric acid, amino acids in urine; effect of temperature on, *1:* 386
milk, composition at various stages of lactation vs. cow and human, *1:* 26; *see also under* "reproduction and sex organs"
morphologic and physiologic characteristics of germfree, *1:* 452
muscle
electrolytes and water in, *1:* 109
electrolytes, Na, K and water content of normal, pregnant, pseudopregnant and fetus, *1:* 284
myoglobin content; effects of altitude and exercise on, *1:* 206
skeletal, glycogen content in pregnancy, *1:* 339
weight, *1:* 230
nervous system, righting reflexes; effect of Mn deficiency, *1:* 462
nutrition and uniformity, *1:* 151; *see also* "food consumption," "food requirement"
nutritional status of mother and ringtail in suckling, *2:* 216
pancreas, weight; effect of temperature; histology, *1:* 456
parathyroid weight; effect of temperature; histology, *1:* 456
parotid gland, weight; effect of temperature on; histology, *1:* 456
physical activity
diurnal, in stabilimeter cages vs. activity wheels, *1:* 175
effects of, *1:* 100, 206, 217
forced; effects, *1:* 314
swimming performance, age, sex variation, *1:* 331
effect of practice, drugs on, *1:* 380
volitional vs. age and experience, *1:* 157
physiology, *1:* 2, 45, 135
compared with multimammate mouse, *1:* 350
pituitary gland, function, *1:* 349
weight
effect of captivity on, species variation, *1:* 7
effect of temperature on; histology, *1:* 456
of inbred; effect of diet on; histology, *1:* 492
of normal, pregnant, pseudopregnant and fetus, *1:* 284
pulse rate, *1:* 101
reproduction and sex organs, *5:* 90, 117
abortion and vaginal blood, *1:* 209
conception, gestation, lactation, growth of young; effect of hormones on, *3:* 66
conception rate, litter, fetus size; effect of antibiotics on, *3:* 49
estrus; effect of light on, *1:* 41; *4:* 16
and pH values of reproductive tract fluids, *1:* 333
fertility, seasonal rhythm, *4:* 47
fetal fluid, placental type, endometrial differentiation, *1:* 267
fetal resorption; effect of temperature on, *1:* 312
gonads, weight, of male and female inbred, *1:* 376
lactation
blood picture and volume of milk, *1:* 334
effect of
diet on, *3:* 62
light on, *4:* 32
fat metabolism and liver in; effect of diet on, *2:* 104
growth of young; effect of light on, *1:* 132
liver growth; effect of food intake on, *1:* 381
mammary gland growth, *1:* 454
milk let-down; effect of oxytocin and ergotamine on, *1:* 244
milk secretion; effect of color of light on, *1:* 105
"milking" gland number and weight of suckling young vs. litter size, *1:* 235
neural supply in inbred, *1:* 237
litter size, *1:* 35, 235; *3:* 49
effect on body weight of young, *1:* 334
effect of diet on, *3:* 62
vs. sex ratio and diet, *4:* 91

Rat (*continued*)
litters without 2nd breeding, *1:* 139
organs, weight; effect of light on, *1:* 41
placenta, glycogen content in pregnancy, *1:* 339
polyspermia, in inbred; effect of time of mating and strain differences in incidence of, *1:* 337
pregnancy
and adrenal and pituitary gland weight, *1:* 284
anxiety in; effect on offspring, *1:* 320
blood, muscle water and electrolyte content in, *1:* 284
body weight in, vs. fetal weight, *1:* 284
fat metabolism and liver in; effect of protein-free diet on, *2:* 104
glycogen in organs in, daily variation, *1:* 339
mammary gland growth in, *1:* 454
repeated, and blood vessel pathology, *2:* 286
vaginal blood in, and abortion, *1:* 209
pseudopregnancy, and adrenal and pituitary gland weight, *1:* 284
period and luteal function after sterile mating, species variation, *1:* 470
reproductive cycle
in inbred, *4:* 52
timetable of events, *1:* 267
reproductive period, fertility, sterility, litter size, sex ratio, of wild gray Norway; effect of captivity on, *1:* 35
seminal vesicle of inbred, weight, *1:* 376
sex hormones; effect on hair growth, *1:* 378
testes, weight, *1:* 230
effect of diet on; histology, *1:* 492
effect of temperature on; histology, *1:* 456
respiration, *1:* 101
anatomy, mechanics, physiology; tables, *1:* 394
constants, *7:* 164
tracings, *1:* 429
volume, of white and cotton, *1:* 72
salivary glands, electrolytes, in secretions, *1:* 497
weight and histology; effect of dental clipping, hypophysectomy, cortisone on, *2:* 369
submaxillary gland, weight; effect of temperature; histology, *1:* 456
skeleton
anatomy of embryo and newborn; x-rays, *1:* 321
development of normal and hypophysectomized; x-rays, histology, *1:* 121
skin
histamine content, of inbred, age variation; effect of weaning, *1:* 186
weight, *1:* 230
spleen
arterial patterns, x-ray, *1:* 338
fat, mineral, protein, water in, age, sex variation, *1:* 89
morphology of, conventional and germfree, *1:* 503
weight, *1:* 76, 230
effect of
diet; histology, *1:* 492
temperature, histology, *1:* 456
stomach
blood content, of mucosa, densitometric measurement, *7:* 150
emptying; effects of temperature on, *1:* 240
volume, contents and emptying time, *3:* 70
weight, *1:* 230
survival of germfree in conventional environment, *4:* 95; *see also* "lifespan"
taste response, to KCl vs. NaCl, etc., *1:* 200
tear secretion after acetylcholine injection, *7:* 70
thymus
mitotic index of lymphocytes, *1:* 402
weight, *1:* 230
effect of
diet on; histology, *1:* 492
temperature on; histology, *1:* 456
thyroid gland
function, *1:* 349
effect of extra handling on, *1:* 194
effect of gentling on, *1:* 258
weight
effect of captivity, species variation, *1:* 7
effect of temperature on; histology, *1:* 456
tongue, weight; effect of temperature on; histology, *1:* 456
urine
constituents, *see under* "kidney function," "metabolism, mineral, protein"
volume
age variation, *2:* 67
effect of altitude and temperature on, *1:* 385, 387
effect of temperature on, *1:* 386, 426
of house and migratory, *1:* 188
use
anatomical research, *3:* 19
drug testing, *6:* 11
germfree in stress and shock research, *2:* 375
inbred
in research, *1:* 151
tumor research, *6:* 49
multimammate in toxoplasmosis research, *2:* 176
rabies diagnosis, *2:* 76
research, *1:* 45, 87; *4:* 2
endocrinologic; value of littermate controls, *4:* 52
nutritional, *1:* 510
psychologic, *1:* 417
toxicity tests, *2:* 336
vitamin D assays, *4:* 90; *5:* 12
vitamins, thiamine synthesis by intestinal microflora; effect of antibiotic on, *3:* 72
water consumption
age variation, *3:* 67
and balance in house and migratory, *1:* 188
effect of
altitude and temperature on, *1:* 385, 387
temperature on, *1:* 312, 386, 426
fasting; effect of altitude, temperature on, *1:* 388
Rearing of young, *see* under Breeding; Feeding
Records
animal colony, *4:* 49
animal supply department, *5:* 32
forms for animal colony, *5:* 123
laboratory animals, *5:* 18, 102
mice, inbred and random bred, *4:* 76
inbred, breeding and tumor incidence in, *4:* 59
monkey health in colony, *8:* 5
rabbit, *5:* 110
colonies, *4:* 115
rats, random and inbred, *4:* 109
specific pathogen-free colony, *4:* 49
Regulations on
see also Legislation
care, housing, handling, sanitation of laboratory animals, *6:* 36
customs report, *6:* 39
impounded animals, *6:* 31, 45
interstate shipment of dogs, *6:* 1
laboratory animals, *6:* 57
international, bulletin on, *9:* 11
purchase of domestic animals, and use in research, *6:* 12
trade practices, for rabbit breeders, *6:* 50
Reptiles
see also Turtle
body, organ, gland weights, *1:* 37
book on, *1:* 257
care and management, *5:* 27, 102, 133
carotid body, sinus, anatomy, macro- and microscopic; embryology, physiology, *1:* 322
circulatory system, *1:* 486

Reptiles (*continued*)
nervous system, anatomy, *1:* 21
skeleton, anatomy; classification, *1:* 257
Respiration measurement techniques
see also " respiration" *under* specific kind of animal
lung function, in dog, *1:* 495
lung function, in goat, *7:* 83
rabbit, newborn, tidal air, *1:* 443
sheep, swine, *7:* 83
small animals, *1:* 429
Respiratory diseases in animals
see also under Diseases; *see also* Lung
induction, experimental, of pneumonia in mouse, *7:* 122
inflammatory response, measurement of, *2:* 328
Respiratory gases, measurement of
see also Metabolism; basal, determination; "respiration" *under* specific kind of animal
in rat, sonic gas analyzer for, *7:* 80
in small animals; CO_2, *7:* 160
Respiratory movement measurement, in small animals, *7:* 136
Respiratory requirement, device providing for, in mouse, *7:* 165
Respiratory volume measurement
in laboratory animals, *1:* 72
in rabbit, *7:* 15
Respirometer, for rat, *7:* 117
Restraint and protective devices and techniques
animals, *1:* 135
and rope techniques, *7:* 33
small, *2:* 69
board, *7:* 29
cat, *5:* 34; *7:* 33
board (stock), *7:* 21
effects on, *1:* 165
cattle, and rope techniques, *7:* 33
chicken, *7:* 33
board (stock), *7:* 5
dog, *7:* 33
bile collection, *7:* 175
board, *7:* 21
effects on, *1:* 196, 264, 344, 363
"Elizabethan" collar, *7:* 111
fox, *7:* 33
guinea pig
board, *7:* 1
effects on, *1:* 419
holder for i.v. injections, *7:* 14
horse, and rope techniques, *7:* 33
mink, *7:* 33
monkey *5:* 61
box, *7:* 154
chair, *7:* 109, 162
effects on, *1:* 362
table and cassette holder for chest radiography, *7:* 120
mouse
cage, *5:* 33
effects on, *1:* 119, 120
holder for i.v. injections, *7:* 14
poultry, *7:* 33
rabbit, *7:* 33, 187
board (stock), *7:* 1, 21, 23
head holder, *7:* 66
rat
bile collection, *7:* 175
board, *7:* 1, 178
cage for i.v. injections, *7:* 24
effects on, *1:* 224, 314, 327, 328, 419, 420, 421, 422, 449; *7:* 178
electric fence, *7:* 61
holder
for i.v. injections, *7:* 14
for measuring blood flow, *7:* 54
i.t. injections, *7:* 59
lifting from cage, *5:* 20
rodents, oral holder for, *7:* 33
squirrel
cage, *5:* 14
electric fence, *7:* 61
swine, and rope techniques, *7:* 33
Resuscitation, *see* Artificial respiration
Rhesus monkey, *see* Monkey
Rhipicephalus sanguineus, *2:* 105
Rockefeller Institute, animal houses, *5:* 63
Rodents
see also Guinea pig; Hamster; Mouse; Rat
adrenal gland weight to body weight relation; statistical analysis, *1:* 128
bladder emptying and physical activity, method for correlating, *7:* 142
body, organ, gland weights, *1:* 37
body weight to adrenal weight relation, *1:* 128
care and management, *5:* 102
conference on diseases in, *2:* 197
feeding behavior, determination of, *3:* 90
reproduction, litters without 2d breeding, *1:* 139
Roundworms, *see* "parasitic, helminth" *under* Diseases

Saccharomycopsis guttulata, *2:* 103
Salamander, development, (film), *1:* 83
Salivary gland function tests, *1:* 298
Salmonella, *2:* 23, 29, 116, 121, 137, 180; *3:* 80
testing method for, *2:* 274
Salmonella enteritidis, *2:* 34, 108
Salmonella Newport, *2:* 40
Salmonella typhimurium, *2:* 154
Sanitation
see also Carcass disposal; Housing
code on, *6:* 12
control of
diseases, *2:* 280
epidemics, in mouse colonies, *2:* 122
disinfection of microbiological laboratories, *2:* 331
incoming animals, *5:* 117
products for animal colony, *5:* 57
small animal practice, *2:* 69
techniques, outline of training course in, application in animal care, *5:* 84
Sarcocystis leporum, *2:* 127
Sarcocystis tenella, *2:* 127
Sarcoptes scabiei, *2:* 320
Schistosoma research, use of multimammate mouse in, *1:* 350
Sciurus ludovicianus, *1:* 473
Scottish terrier, *1:* 264
Seasons, effects of, *see* Temperature
Sedatives, for cat, dog, *2:* 213
Semen collection techniques
dog, *4:* 106
electro-ejaculation, guinea pig, *4:* 86
rabbit, Dutch, *4:* 88
Serologic service, distemper immunity in dogs, *2:* 195, 292
Serologic studies, use of mouse, inbred, in, *4:* 53
Serologic tests, *1:* 229; *2:* 47, 199; *7:* 81
complement fixation, for *H. muris* and *E. coccoides*, *2:* 289
distemper in dogs, *2:* 142, 195, 303
flocculation, for trichinosis, *2:* 189
fluorescent antibody, for distemper, infectious hepatitis, *2:* 142
indirect, in fungal disease, *2:* 283
hemagglutination
for infectious canine hepatitis, virus antibodies, *2:* 205
for toxoplasmosis, *2:* 171
leptospiremia, use of chicken in, *6:* 24
leptospirosis, *2:* 195, 270
mycoses, in laboratory animals, *2:* 73, 283
toxoplasmosis, *2:* 138, 171

Serologic tests (*continued*)
trichinosis, *2:* 189
tumors, virus-induced, *2:* 228
virus hepatitis in dog, *2:* 142, 195, 205
flocculation vs. precipitation, *2:* 157
Sex determination methods
in animals, *1:* 427
in mice, newborn, *1:* 313
Sheep
adrenal glands, anatomy; histology, *1:* 489
blood
hematology, *1:* 71, 403, 445; *2:* 47
hemoglobin, sulfhydryl groups in; genetics of, *1:* 392
proteins in serum, *1:* 506
blood types, *1:* 467
body fat, of lamb, density, *1:* 142
body weight, at birth; genetic effects, *1:* 227
bone marrow, cytology, *1:* 403
fetal fluid, placental type, endometrial differentiation, *1:* 267
food consumption, *3:* 34
food requirements, *3:* 35
food and water consumption, *3:* 1
effect of temperature on, *1:* 312
hair, growth, replacement, type, *1:* 99
immune bodies
antibodies in blood, complement, titer, *1:* 229
antigens in blood, *1:* 467
liver
biochemistry vs. body weight, *1:* 221
weight, *1:* 221
metabolism, basal, *1:* 221
effect of temperature on, *1:* 312
milk, composition of, *3:* 42
reproduction, *1:* 438
insemination with mixed semen; effect on weight of offspring, *1:* 227
use in insecticide tests, *6:* 46
Sheffield University animal house, *8:* 9
Shepherd, German, *2:* 96
Shetland sheep dog, *1:* 96, 363
Shock
effect on dog, *1:* 344
effect on rat, *1:* 258, 314, 411; *2:* 151
Shrew (*Sorex cinereus cinereus*), metabolism, basal, *1:* 66
Skin
absorption, study of, in rat, *7:* 70
disease research, use of dog in, *2:* 351
exposure techniques
see also Ear chamber technique
for blood-sucking arthropods in rabbit, *7:* 35
scalding technique for mouse and rat, *7:* 181
grafting techniques in mouse, *7:* 39
joining of two animals, *see* Parabiosis
tests
for mycoses in laboratory animals, *2:* 73
for parasites, *see under* Parasites; *see also* "parasitic (diagnosis)" *under* Diseases
for sarcosporidioses in guinea pig, *2:* 127
Smith, Kline and French Laboratories, animal colony, *5:* 89
Social behavior in animals, *see* "behavior patterns" *under* specific kind and groups of animals
Soporific drugs, for cat, dog, *2:* 213
Sound proofing, *see* Noise control
Sources of supply
cat, *9:* 7
Gt. Britain, *6:* 26
chicken, Gt. Britain, *6:* 40
dog, *6:* 31; *9:* 9
Baltimore, *6:* 32
Gt. Britain, *6:* 26
guinea pig, *4:* 45; *5:* 125
bulletin on, *9:* 17
Gt. Britain, *6:* 40
hamster, *4:* 45
bulletin on, *9:* 17
laboratory animals, *4:* 40
accredited, Gt. Britain, *6:* 25
bulletin on, *9:* 11, 17
catalogue, *6:* 58
legislation and standards, *6:* 63
organizations, standards, *6:* 19
standards, *6:* 39
monkey, *5:* 67
mouse, *4:* 45
audiogenic seizure susceptibility, *4:* 36
bulletin on, *9:* 12, 17, 19
Gt. Britain, *6:* 40
inbred, *9:* 15
mutant gene, *1:* 245
pig, miniature, *4:* 61, 74
rabbit
bulletin on, *9:* 17
Gt. Britain, *6:* 40
rat, *4:* 45
bulletin on, *9:* 17
Gt. Britain, *6:* 40
watering equipment, *5:* 116
Soybean forage, estrogenic activity of, *3:* 71
Space research techniques
chamber for mouse, *7:* 179
in monkeys, *7:* 162
Sparrow, *1:* 9
Spaying, *see* Castration
Specific gravity measurement of body of guinea pig, by air displacement, *7:* 138
Spermophile, anatomy, physiology, hematology, spontaneous diseases, *1:* 135
Spinal fluid
collection techniques, in dog, *1:* 207, 424
in dog, *2:* 183
Splenectomy
effect on dog, *1:* 184, 214; *2:* 296, 314, 342
effect on rat, *2:* 311
Splint, for mouse, *7:* 39
Squirrel
see also Spermophile
blood, electrolytes, *1:* 317, 398
hair growth, in lactation, of Asiatic, *1:* 472
handling of, *5:* 14; *7:* 61
porphyrins, enzymatic synthesis in urine, *1:* 473
Stabilimeter cage for rat, *1:* 175
Standards for
animal care, *6:* 27, 33, 63
hamster, *4:* 10
inbred mouse production, *4:* 65, 76
inbred rat production, *4:* 109
Staphylococcus aureus, *1:* 504; *2:* 41, 218, 332
Starvation; effect of, *see* Food deprivation, restriction
Statistical analysis
behavior in dogs, *1:* 144
blood counts, *1:* 8, 78, 82, 91, 104, 383
blood volumes, circulating, *1:* 480
body, brain, spinal cord weight and length, *1:* 86
body weight, length, vs. endocrine gland weight of rat, *1:* 52
electrocardiograms, age variation, in rat, *1:* 358
emotional defecation, *1:* 158
fertility, maternal age selection, *4:* 103
genetic variability in physiological constants, in dogs, *1:* 96
methods, *7:* 81
Sterilization
see also Disinfection; *under* Housing; Sanitation
air, with U.V. light in microbiologic disease laboratories, *5:* 71, 82, 92

Sterilization (*continued*)
bedding, for germfree animals, *5:* 129
cages, *5:* 17
equipment, *5:* 1
breeding colony, *4:* 13
conducted heat, *5:* 112
disease-free colony, *5:* 105
dry heat; standards, *5:* 111
economics in, *5:* 8
food, *5:* 109
by autoclaving, *4:* 31
for disease- or germfree colonies, *5:* 17, 105, 129
equipment, *5:* 100
Stimulants, metabolic, use of guinea pig in research on, *1:* 371
Streptobacillus moniliformis, *2:* 264; *4:* 19
Streptococcus, hemolytic, *2:* 41
Streptococcus liquefaciens, *3:* 78
Streptomycins, therapeutic use in animals, *2:* 42, 153
Stress
see also Diseases; *also under* Handling; Population; Restraint; Temperature; for effects of lactation, pregnancy, *see under* "reproduction and sex organs" *under* specific kind of animal
effects on
monkey, *1:* 40
mouse, *1:* 133
rat, *1:* 197; *2:* 286
shock studies, use of rat in, *2:* 375
steroids to diagnose latent *Salmonella* infection, *2:* 274
study techniques
for rat, *7:* 178
for small animals, *7:* 168
Strongyloidiasis, *see* "parasitic, helminth" *under* Diseases
Sugar cane, as bedding for animals, *5:* 28
Sulfonamides, in control, treatment of disease, *2:* 31, 77, 78, 131, 152, 159, 203, 206, 237
effect on rat, *3:* 41
tolerance of mouse for, *2:* 203
Supply department
management of, *5:* 18
records, personnel for, *5:* 32
Surgery, books, *2:* 178; *7:* 172
Surgical techniques, *2:* 83
on animals, *2:* 353; *7:* 172
brain stem transection, in dog, *7:* 50
on dog, *1:* 481; *2:* 178; *7:* 182
vocal cord removal, *7:* 18
on mouse, rectal replacement, *2:* 310
operating board for small animals, *7:* 16
operating stand, *7:* 9
operating theater, construction design, *5:* 44
Swelling, *see* Edema
Swine
see also Animals; Breeding; Diseases; Domestic animals; Handling; Housing; Pig, miniature
adrenal glands
anatomy, *2:* 219
histology, *1:* 489
blood
hematology, *1:* 12, 71
proteins in serum, *1:* 382
of adult, newborn, young, *1:* 506
blood pressure, *1:* 368
blood types, *1:* 467
body, chemical composition of, age, sex variation, *1:* 89
body fat, *1:* 89, 142
books on, *2:* 219; *3:* 42
enzymes, glutamic oxaloacetic and pyruvic transaminases in serum and tissues, *1:* 439
fetal fluid, placental type, endometrial differentiation, *1:* 267
food consumption, *3:* 1, 34
food requirements, *3:* 35, 56
of sow and breeding boar, *3:* 36
hair, growth, replacement, type, *1:* 99
immune bodies
antibodies in blood, complement, titer, *1:* 229
antigens in blood, *1:* 467
metabolism, fat, mineral, protein, age, sex variation, *1:* 89
milk, composition of, *3:* 42
physiology, *2:* 219
reproduction, *1:* 438
pregnancy, lactation; food requirements and mortalities of young in, *3:* 36
use, in rheumatoid arthritis research, *2:* 253
water consumption, *3:* 1
Symposia, *see* Conferences
Syphacia obvelata, *2:* 190

Tadarida braziliensis mexicana, *2:* 187
Tapazole, effect on rat, *1:* 161
Tapeworms, *see* "parasitic, helminths" *under* Diseases
Taste
measurement techniques, in cat, *3:* 39
response, in animals, species variation, *1:* 200
Teeth, clipping of
effect on rat, *2:* 369
examination techniques, for rodents, *7:* 38
system for recording conditions in hamster, *1:* 156
Television, on hamster, *1:* 325
Temperature, physiologic effects of
for body temperature, *see under* specific kind of animal; *see also* Body temperature measurement techniques; for requirements in housing, *see under* Housing ("temperature," "environmental requirements"); *see also* "physical agents" *under* Diseases; Environment
environmental, on
animals, *1:* 59, 169; *5:* 19
animals, vs. body size, genetics, *1:* 146
cattle, *1:* 379, 455
chicken; seasonal, *3:* 58
rabbit; seasonal, *3:* 15, 379
rat
geographical, and tumor incidence, *2:* 229
seasonal, *3:* 12
high, on
animals; tropical climate, *1:* 6
cattle, *1:* 307, 379
dog, *3:* 21
guinea pig, *1:* 31
tolerance for, *6:* 41
hamster, *1:* 361
monkey, and effect of restraint, *1:* 362
mouse, *1:* 15, 36, 116, 298, 330; (and humid) *1:* 16, 23
and resistance to infection, *1:* 47
tolerance for, *6:* 41
rabbit, *1:* 306, 307, 379
and adaptation to, *1:* 14, 312
rat, *1:* 138, 240, 347, 385, 386, 387, 389, 456; *2:* 13; *3:* 10
adaptation to, *1:* 312, 448
effect of restraint, stress, *1:* 449; *2:* 151
longevity, *1:* 195, 449; *2:* 151, 302
protection against, *1:* 351
tolerance for, *6:* 41
sheep, and adaptation to, *1:* 312
low, on
animals, *1:* 440
cat, and effect of restraint, *1:* 165
dog, *1:* 154, 248, 250
resuscitation after freezing, *1:* 396
guinea pig, *1:* 262
effect of restraint, *1:* 419
hamster, *1:* 238, 360, 460
resuscitation after freezing, *1:* 396
marmot, *1:* 122

mouse, *1:* 15, 16, 36, 116, 120, 298, 330
adaptation to, *1:* 16
critical point for nervous function, *1:* 425
effect of restraint, anesthesia, *1:* 119
resuscitation after freezing, *1:* 396
sensitivity of obese to, *1:* 173
rabbit, *1:* 505
and adaptation to, *1:* 14
rat, *1:* 86, 241, 385, 386, 387, 389, 426, 456, 458; *2:* 151; *3:* 10
adaptation to, *1:* 199, 300, 448
effect of restraint, *1:* 224, 327, 419
protection against, *1:* 351
resistance to, in caged vs. free-roaming, *1:* 422
resuscitation after freezing, *1:* 396
neutral, on
mouse, *1:* 116, 330
rat, *1:* 386, 387, 389, 456; *2:* 151; *3:* 10
response to drugs and chemical agents of
animals, *1:* 59; *6:* 37
mouse, *1:* 498; *2:* 10
rat, *2:* 336
Temperature choice by frog; recording techniques, *7:* 12
Thermoregulation in animals, *see* "body temperature" *under* specific kind of animal; *see also* Temperature
Thoracotomy techniques, and chest closure, in dog, *7:* 182
Thyroid function techniques, *see* "thyroid gland" *under* specific kind of animal; *see also under* Radioisotope techniques
Ticks, diseases by, *see* "parasitic, arthropod" *under* Diseases; *see also* Parasites, "external"
Tinea capitis, *see* "fungal (ringworm)" *under* Diseases, *2:* 323
Tissue chamber, for skin grafts in mouse, *7:* 39
Tissue culture techniques, *1:* 427
chamber for phase microscopy, *7:* 190
tumors, *1:* 83
use in research instead of animals, *7:* 107; *8:* 16
Tissue fluid measurement, in dog, *1:* 166
Tissue grafting, use of inbred mouse in, *4:* 53; *see also* Parabiosis
Toad
see also Amphibia, Frog
blood serum, bile, liver, cholesterol, *1:* 474
Toxicology, 7: 164
see also Pharmacologic research
books on, *2:* 162, 347
control animals, observations on, *2:* 51
effects of chemicals consumed by laboratory animals in diet vs. man, *3:* 34
intravenous infusion in inbred mice and measurement of effect, *7:* 134
research
methods and interpretation, *7:* 64
use of rat in, *2:* 336
techniques, *7:* 81; *see also* Feeding; Infusion; Inhalation; Injection
Toxocara, disease caused by, *see* "parasitic, helminth" *under* Diseases
Toxocara canis, *2:* 278, 284
Toxoplasma, *2:* 78, 159, 160, 176, 297, 359
Toxoplasma (RH strain), *2:* 263
Toxoplasma gondii, *2:* 130, 152
Toxoplasmosis research, use of multimammate rat in, *2:* 176
Tracer techniques, *see* Radio isotope techniques
Training of personnel, *see* Personnel
Tranquilizers
effect on behavior in rat and monkey, *7:* 155
effect on laboratory animals, *2:* 347
screening tests, use of small animals in, *7:* 143
Transplantation of organs and tissues, *7:* 172
Transportation of
see also Carrying techniques
animals, *5:* 27; *9:* 11
carts for, *5:* 59
committee on regulation of, *6:* 57
international regulations, *6:* 39
sanitation of railway cars, *6:* 43
standards on, *6:* 19
wound incidence, *2:* 367
cat, *5:* 34
carrier for, *6:* 21
dog
carrier for, *6:* 21
regulations on, *6:* 1
standards on, *6:* 59
germ-, or specific pathogen-free animals, *4:* 78; *5:* 109
plastic isolators for, *4:* 114
guinea pig, *5:* 28
tolerance to high humidity, temperature, *6:* 41
hamster, *4:* 10
monkey, *2:* 97; *5:* 67, 96
by air, regulations, *6:* 35
cynomolgus, *6:* 52
mouse, *5:* 28
specific pathogen-free, *5:* 109
tolerance to high humidity, temperature, *6:* 41
rabbit, *5:* 28
rat, *4:* 2; *5:* 28
and effect, *1:* 314
pathogen-free, *5:* 109
tolerance to high humidity, temperature, *6:* 41
Trapping
of laboratory animals, *5:* 44
of monkeys, *2:* 97
Traps, for squirrel, *5:* 14; *7:* 61
Treatment of disease, *see under* Diseases; Drugs
Treponema, *2:* 116
Trichinella, *2:* 214
Trichinella spiralis, *2:* 374
Trichloroethylene, *see under* Anesthesia
Trichophyton mentagrophytes, *2:* 163, 217, 227, 248, 309, 335
Trimethoxybenzoyl-glycine-diethylamide, sedative effect on cat, dog, *2:* 213
Trypanosoma, *2:* 143, 359
Tubercle bacillus, *2:* 324
Tuberculosis tests
in monkey, *2:* 7, 30
standard operating procedure, *5:* 123
in poultry, *2:* 226
use of guinea pig in, *5:* 97
Tumors
books, *2:* 16, 25, 65, 88, 221
in animals, *see under* Diseases
Turkey
see also Birds; Domestic animals; Poultry
cholinesterase in blood, *1:* 219
food requirements, *3:* 35
food and water consumption, *3:* 1
hematology, *1:* 71
Turtle, *see under* Diets; Diseases; Housing; Reptiles

Ultraviolet light, in animal houses
see also under Disinfection; Housing; Sterilization
effect on captive marmoset; reproduction, *2:* 168
Uncinaria stenocephala, *2:* 312
UNESCO, committee on laboratory animals, *6:* 39
Ungulates, body, organ, gland weights, *1:* 37; *see also* Horse
U. S. Air Force, chimpanzee colony, *5:* 61
U. S. Army Chemical Center, disease-free rat colony, *4:* 49
U. S. Army Medical Nutrition Laboratory, *2:* 366
U. S. Congress Bill on poundmasters' functions, *6:* 20
U. S. Dept. of Agriculture, Bureau of Animal Industry, *1:* 195; *2:* 37
U. S. Rabbit Experiment Station, *4:* 18
Universities Federation for Animal Welfare, activities, *8:* 16
book on laboratory animals, *5:* 102
history, *8:* 6

University of California, rules on animals, *6:* 12
University of Minnesota, Hormel Institute, *4:* 74
University of Texas, chimpanzee colony, *5:* 61
Urethane, *see under* Anesthesia
Urinary bladder pouch technique, in dog, *7:* 116
Urine
  analysis
    see also "Kidney" *under* specific kind of animal
    chemical, *2:* 47; *7:* 81, 105
    paper strip test, *7:* 125
    urea, *7:* 146
    urobilinogens, *2:* 145
  collection techniques, *1:* 68
    see also Metabolism cages
    in rat, *7:* 24
      cage for, *5:* 31
      flow measurement, *7:* 45
      separator for, *7:* 84
    in rodents, equipment, *7:* 142
  measurement techniques, in rat, mouse, dog, monkey, *5:* 69
  moisture loss determination, in cattle and rabbit, *1:* 379

Vaccine tests for brucellosis
  for vaccination in disease prevention, *see under* Diseases
  use of guinea pig in, *6:* 16
Ventilation in animal houses, *see under* Housing
Vertebrates
  books on, *1:* 21, 267; *4:* 112
  nervous system, *1:* 3
Virology, *see* Microbiologic research
Viruses, books on, *2:* 114, 301
Vision, *see* Eyes
Visual aid techniques, sketching from slide, *1:* 55; *see also* Films; Television
Vitamin assays
  tests, *1:* 406; *7:* 164
  use of animals in, *4:* 90; *5:* 12
Vitamin supplements, and effects, *see under* Dietary supplements
Vitamins, toxicity for monkey, *2:* 174
Vivisection, *see* Animal experimentation; Humane treatment
Vocal cord removal, in dog, *7:* 18

Walter Reed Army Institute of Research, *4:* 70, 82
Waste disposal, in germfree colony, *5:* 129; *see also* "sanitation" under Housing
Water, *see* "body water" *under* specific kind of animal; Body water measurement
Water intake measurement
  see also "water consumption; requirements" *under* specific kind of animal
  equipment for, *5:* 53
  in laboratory animals, *5:* 69
Water loss determination, *1:* 379
Watering devices for
  animals, *5:* 5, 53, 123, 132
    automatic, for cages, *3:* 84
    bottle holder, *4:* 38
    cost and source, *5:* 116
  guinea pig, *5:* 132
  mouse, *4:* 13; *5:* 37, 131
  rabbit, domestic, *4:* 58
  rat, *5:* 12, 37
    standards, *4:* 109
Wheel cage apparatus, for rat, *1:* 157, 175
Wire-haired fox terrier, *1:* 96, 363
Worms
  nervous system, *1:* 3
  parasitic, *see* "parasitic, helminth" *under* Diseases

X-rays, *see* Radiology

Yeasts, characteristics of, *2:* 114

Zonotrichia leucophrys gambelii, *1:* 140
Zoonoses, *see* "transmitted to man" *under* Diseases, in animals; "health hazards" *under* Personnel